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OCCUPATIONAL HEALTH IN THE CHEMICAL INDUSTRY

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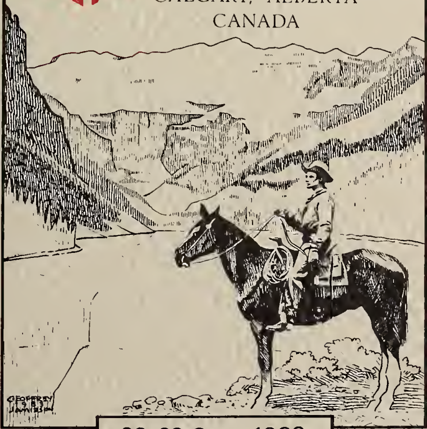

26-29 Sept. 1983

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Occupational Health in the Chemical Industry

Proceedings of the Eleventh
International Congress on
Occupational Health in the Chemical
Industry, September 26 - 29, 1983,
Calgary, Alberta, Canada
Organized by the MEDICHEM
Calgary '83 Association

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MEDICHEM Calgary '83 Association

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ISBN 0-9691834-0-2

Published 1984 by
MEDICHEM Calgary '83 Association
5th Floor, 10709 Jasper Avenue,
Edmonton, Alberta, Canada
T5J 3N3

The responsibility for opinions expressed in the articles, studies and other contributions herein rests solely with their authors, and publication does not constitute an endorsement by the MEDICHEM Calgary '83 Association.

Printed in Canada by GTO Quick Print & Copy Ltd.

TABLE OF CONTENTS

TABLE OF CONTENTS

Page

FOREWARD 1

ACKNOWLEDGEMENTS 2

OPENING ADDRESSES

Hon. Frank Lynch-Staunton
Lieutenant-Governor, Alberta 5

Hon. Bill Diachuk, Minister Responsible for
Alberta Workers' Health, Safety and Compensation 7

Prof. Dr. Alfred M. Thiess, MEDICHEM Chairman 11

TECHNICAL REPORTS AND PAPERS

THEME I - OCCUPATIONAL HEALTH AND TOXICOLOGICAL PROBLEMS IN THE PETROLEUM, GAS AND PETROCHEMICAL INDUSTRIES

Occupational health and toxicological problems in the petroleum, gas and petrochemical industries. R.E. ECKARDT 19

Renal toxicity and carcinogenicity of petroleum hydrocarbons in rats: a critical analysis. L. GOLBERG 31

An evaluation of possible effects on health following exposure to ethylene oxide.
G.W. RICHMOND, R.H. ABRAHAMS, J.H. NEMENZO, and C.H. HINE 47

Reactions dermatologiques dans l'industrie des fibres synthétiques. A. SCHAFRIR and A. SCHAFFER 63

Formaldehyde sensitivity following exposure to building materials.
D.E. SPRAGUE, W.J. REA, R.E. SMILEY, A.R. JOHNSON, W.F. TUCKER and E.J. FENYVES 71

Page

Limites d'évaluation des risques de la pollution de l'air: concentrations physiologiques en polluants gazeux dans l'air expiré. E. FOURNIER 73

Le développement des tests de biotoxicologie pour une meilleure connaissance des métabolismes et des effets de synergie des polluants chimiques. J. CHALABREYSSE, M. ARCHIMBAUD, E. ANSOBORLO, M.H. HENGE-NAPOLI and G. BOURGINEAU 93

Peripheral sensory irritation as a factor in defining workplace exposure guidelines. B. BALLANTYNE 119

Particulate oil shale inhalation and pulmonary inflammatory response in rats. J.S. WILSON, L.M. HOLLAND, E.MARTINEZ, G.C. SAUNDERS and M.S. HALLECK 151

The effects of hydrogen sulphide on excitable tissues. J.C. DONINI and J.F. BECK 163

The genotoxic effect of epichlorohydrin on mice as estimated by the micronucleus test. Y.F. WANG and C.H. HINE 175

THEME II - EMERGENCIES IN THE CHEMICAL INDUSTRY: ASSESSMENT AND INTERVENTION

Emergencies in the chemical industry: assessment and intervention. A.M. THIESS 185

Acute respiratory reactions to chemical exposures: focus on oxides of nitrogen. M.R. BECKLAKE 207

L'apport d'un laboratoire d'hygiène industrielle aux médicins du travail lors d'un accident d'origine chimique. J. CHALABREYSSE, F. TEULON, A. TREGOURES, R. BERTRAND, G. GARNIER and C. ROUSSEL 215

Analysis of an explosive accident in a VCM plant. L. DJERASSI 227

A linked agromedical model for the assessment, intervention, and prevention of an occupational and related pesticide injury. R.S. LEVINE, J.E. DAVIES, V.H. FREED, and J.I. GRIESHOP 229

The possibilities of accidents with chemical substances - their effects on human beings and the necessary emergency measures. H.J. FROST and J. STEINBORN 237

Page

Why a discussion about "intoxications through nitroglycol" again? H. SYMANSKI 255

THEME III - APPLICATIONS OF COMPUTER TECHNOLOGY IN OCCUPATIONAL HEALTH

Computers in occupational health: present and future applications and concerns for information and advice. G. ATHERLEY, P. GALLINA and I. RODIN 261

Computers and information needs in occupational medicine. F.R. SMITH 283

Integrated computerized collection in occupational medical, ambient and biological monitoring data in the chemical industry. U. KORALLUS, P. HARTMANN and H.G. SCHALK 291

Application of a computerized occupational health and environmental surveillance system (COHESS) to employees in chemical production. M. CHELSKY 305

"Hydro health" the Norsk Hydro system for processing administrative-epidemiological data. K.J. KORSGAARD and O. OYSTEIN 315

A user-driven occupational health information system. N.E. GIBSON, E. MASTROMATTEO, E.S. GIBSON and C.W. TERRY 331

Computer based information system for unpublished literature. S.A. MARSHALL, D.J. MARSICK and T.A. TOWERS 341

Occupational health information systems - functional requirements and design issues. W. RAPPAPORT and D. OLIVER 351

THEME IV - CURRENT OCCUPATIONAL HEALTH PROBLEMS IN THE CHEMICAL INDUSTRY

Current occupational health problems in the chemical industry. E. MASTROMATTEO 365

Occupational exposure to cadmium and the excretion of β_2-microglobulin. W. RIETH, F. FELIXBERGER and D. SZADKOWSKI 387

Page
Respiratory effects of formaldehyde in the sheepskin processing industry. C.M. BISHOP 401

Studies on the structure-toxicity relationship of industrial chemicals. K. HASHIMOTO, H. TANII, J. SAKAMOTO and H. TSUJI 423

An evaluation of the relationship between the acute irritancy potential of topically applied chemicals in the rabbit and man. J.R NETHERCOTT, E.R. MARAGHI and D. ANDREWS 427

Long-term effects of organic solvents. P. ORBAEK, B. HAEGER-ARONSEN, U. HJORTSBERG, J. RISBERG, I. ROSEN, S. HAGSTADIUS, G. REGNELL S. REHNSTROM, K. SVENSSON and H. WELINDER 437

Chronic intratracheal toxicity of manganese monoxide, manganese dioxide in rabbits. E. NAKAYAMA and S. IMAMIYA 447

Biological and clinical monitoring of workers of a plant producing alcohols with cobalt hydrocarbonyl based catalyst. G. ARMELI, R. MATTIUSSI, G. DELEIDI and R. TERRANOVA 449

Incidental uptake of digitalis and quinine in chemical workers. H. RECKENDORF, E. BESENFELDER, V. HRSTKA and K. REIFF 465

Pulmonary function study on workers with long-term exposure to chlorine. H. KROTZSCH and F. SCHUCKMANN 475

A five year study of ionizing radiation exposure at a fertilizer manufacturing facility. H.E. SIEGEL, I. DRUMMOND and G.A. SAUNDERS 485

Mutagenicity of some aniline derivatives. H. SHIMIZU and N. TAKEMURA 497

CLOSING ADDRESS

Prof. Dr. Alfred M. Thiess, MEDICHEM Chairman 509

PARTICIPANTS & COMMITTEES

Participants 515
Committees 517

FOREWARD

MEDICHEM is an international scientific group of medical doctors working on medical problems in the chemical industry, the Board of which is a scientific committee of the Permanent Commission and International Association of Occupational Health. The objective of MEDICHEM is to promote, within the framework of the Permanent Commission, cooperative efforts for the solution of occupational health problems arising in the chemical industry.

In September, 1983, the Eleventh International MEDICHEM Congress on Occupational Health in the Chemical Industry was held in Calgary, Alberta, Canada. A wide variety of papers concerning the prevention and treatment of occupational disease and injury associated with exposure to chemicals were presented and discussed. Particular emphasis was placed on problems in the petroleum, gas and petrochemical industries, emergencies in the chemical industries, and applications of computer technology in occupational health.

The Eleventh MEDICHEM Congress was organized by the MEDICHEM Calgary '83 Association, which is also responsible for the publication of these proceedings. The scientific program was planned and organized by a ten member committee ably chaired by Dr. John Cowell, and by an International Advisory Committee of MEDICHEM Board Members. The generous support of the Government of Alberta and the many sponsoring industries and institutions identified in the list of contributors is gratefully acknowledged. I would also like to express thanks to the many individuals without whose time and effort the Congress and these Proceedings would not have been possible.

R. Orford
General Congress Chairman

ACKNOWLEDGEMENTS

The organizers of MEDICHEM '83, XIth International Congress on Occupational Health in the Chemical Industry, would like to acknowledge the contributions made by the following organizations, without whom the Congress would not have been made possible:

Government of the Province of Alberta
Alberta Workers' Health, Safety and Compensation
Travel Alberta
Alberta Government Services
Alberta Government Protocol Office
Canadian Centre for Occupational Health and Safety
Conventions Plus Consultants
Nova, An Alberta Corporation
Mobil Oil Canada Ltd.
Imperial Oil Ltd.
University of Calgary
Shell Canada Resources
Dome Petroleum Ltd.
Gulf Canada Ltd.
Petro-Canada Exploration Ltd.
C-I-L Inc.
Dupont of Canada Ltd.
Dow Chemical Company of Canada Ltd.
Canadian Superior Oil Ltd.
City of Calgary
Calgary Tourist and Convention Bureau
Oilweek
Frosst
Rocky Mountain Visitor
Glenbow Museum

OPENING ADDRESSES

OPENING ADDRESS

The Honourable
F. Lynch-Staunton
Lieutenant-Governor
Alberta, Canada

I am pleased to welcome you to Alberta at this, the beginning of the MEDICHEM '83 Congress.

A great deal of work is being done throughout the year on research . . . research that will improve occupational health for workers in the chemical industry. We are pleased that you have chosen Calgary as the location to share the results of this research with your colleagues in Canada and those from around the world who are here today.

I trust that each of you will benefit from the congress and will return to your homelands with warm and fond memories of Canada and Alberta.

OPENING ADDRESS

The Honourable
B. W. Diachuk
Minister Responsible for
Workers' Health, Safety and Compensation
Alberta, Canada

It is indeed my pleasure today to bring you greetings along with the Lieutenant-Governor, on behalf of the province of Alberta. It is our sincere wish that this XIth International Congress on Occupational Health in the Chemical Industry will be fruitful for each of you, and beneficial to the world as a whole.

For many of you, this may not be your first visit to Alberta. You may have joined us for the Commonwealth Games in Edmonton in 1978, or more recently at the World Student Games in Edmonton this year.

To all of you, the people of Alberta offer a warm welcome and hope that you will return, possibly for the Olympics, to be held in southwestern Alberta in 1988.

It is fitting that this particular congress is being held here in Alberta, and that you have chosen as the first of your themes "Occupational Health and Toxicological Problems in the Petroleum, Gas and Petrochemical Industries".

Eighty-five percent of Canada's oil and natural gas is presently being produced in this province. There are huge reserves of coal, natural gas and oil. The Alberta oil sands provide one of the richest and abundant sources of synthetic fuel in the world.

I think it's fair to say that we lead the world in the technological beneficiation of sour gas, and in the production of crude oil. Many petroleum and gas explorations as well as petrochemical processes have had to have been adapted for operation in our hostile northern climate, and there have been advances in many other areas, such as the monitoring and control of gas transmission using the latest in computer technology.

However, it is not enough for society to be a leader in technological development. It is not enough for society to progress at any cost. There must be protection built into the system. Who is responsible for seeing that this is done?

I believe there is a shared responsibility for seeing that the health of workers is protected. It is not something just government can, or should see to. And, no, it is not just the responsibility of the employer or the worker. All three must play a role in seeing that occupational health and safety standards are developed and met. All three working together, must see that the potential effects of new technology are recognized early and see that steps are taken to minimize or eliminate them.

Our objective in government is to act as a catalyst, to bring the parties together to work out solutions to the many problems or potential problems that arise whenever and wherever technology is at work. I will admit we all have our hands full in the years ahead.

A good deal of co-operation . . . research and communication by people such as you in this room today is needed to keep abreast with progress in technology. The needs for occupational health and safety research today are great. The needs of tomorrow will be even greater.

Everyday, new devices, chemicals and processes are being created. In many cases, there are associated hazards, with the worker usually being at the greatest risk. Steps must be, and in many cases have been taken to reduce or eliminate these hazards.

For example, asbestos was once thought to be an irreplaceable resource. In recent years, it has borne bitter fruit. In many parts of the world, including Alberta, strict measures have been introduced to control exposure to asbestos. Safer substitute substances have been introduced for many of its applications.

We cannot stop progress, but from time to time we have to step aside to take a serious look at our priorities. Billions of dollars are being spent on research and development of products and processes. In most cases, not enough is spent in looking at the other side of the coin--the possible detrimental effects of the product or process. These issues must be addressed by society. That is why this congress, which looks at that "other side of the coin", is so important.

The exchange of information and ideas between professionals such as yourselves in the field of occupational health is essential. We have many occupational health concerns in common internationally, and must work together to find solutions.

I would like to encourage you, however, to also remember the workers and the public, and their needs for information. The results of medical and toxicological research in occupational health must not remain a mystique. Where hazards exist, they must be made known, in terms that can be understood by those who are affected by those hazards. Where solutions to problems are found, they must be applied, not just written down in library volumes to gather dust for years, or even, as in the case of asbestos, for decades.

At the same time, I think that it is important not to give the impression that you have all the answers when you don't. Too much credibility has been lost by both industry and government by statements denying that health or safety problems exist when what is really meant is that you don't know or that you have insufficient information to make a definitive conclusion.

If you make these things clear, I believe that you will be successful in invoking the help of the public, and in developing a climate of patience and support.

Despite its many adverse effects, technology itself is helping us move towards these goals of the sharing and application of knowledge and information both between professionals themselves and between professionals, workers and the public. State of the art communications now allow us to tie several countries together in visual and voice contact, via satellite. Computers allow us to access vast amounts of information. I understand that some examples of this will be displayed and discussed at this congress.

Communications technology and computerization has given us a tremendous ability to identify and solve our problems. We must do this together. Internationally, we must share data on materials which are hazardous to workers and to our environment. We must pool our efforts . . . you country and ours . . . to ensure healthier and safer work places in the future.

International organizations such as the World Health Organization, The International Labour Organization and the International Permanent Commission on Occupational Health and Safety help this to happen. International communication is taking place and we must ensure that it is continued and strengthened.

We must continue to develop methods of identifying health hazards. We must continue to educate. Most of all we must cooperate. We must work together in solving health and environmental problems. Pollution knows no boundaries! Health hazards know no boundaries! They are universal problems. We must take a united approach to solving them. We must protect our most valuable resource, human life.

U.S. president John F. Kennedy once said, "Let both sides seek to invoke the wonders of science . . . instead of its terrors. Together let us explore the stars, conquer the deserts, eradicate disease, and tap the ocean depths." To that I would like to add, "But let us use science responsibly, and for the good of all mankind."

OPENING ADDRESS

OCCUPATIONAL HEALTH AND TOXICOLOGICAL PROBLEMS IN THE PETROLEUM, GAS AND PETROCHEMICAL INDUSTRIES - EMERGENCIES AND COMPUTER TECHNOLOGY IN OCCUPATIONAL HEALTH IN THE CHEMICAL INDUSTRY

A. M. Thiess
MEDICHEM Chairman

Ladies and Gentlemen,

Two years ago precisely, in Cairo and in Aswan, Dr. Orford opened two heavy suitcases stuffed with interesting travel folders on Canada and handed over to the Board of MEDICHEM a kind invitation extended by the Honourable Peter Lougheed, the Premier of Alberta, the Honourable Bill W. Diachuk, Minister responsible for Alberta Workers' Health, Safety and Compensation and the Canadian Centre for Occupational Health and Safety, and by the Honourable Ralph Klein, Mayor of Calgary, to hold a MEDICHEM Congress in Calgary. This invitation has not only been a warm one - it has also been confirmation of great interest and excellent support and, as first-class organization has also been offered, it was very easy for us to make an immediate decision to accept it. The kind invitation has been heard all over the world, and so today we can welcome colleagues from many countries. On behalf of the MEDICHEM Board, I take pleasure in welcoming you all here in Calgary.

It is an honour for me to welcome especially and to express my deep thanks to the Patron of this international congress, the Honourable Frank Lynch-Staunton, Lieutenant Governor of Alberta, who, by his presence, emphasizes the importance of our conference.

I should also like to welcome, on behalf of you all the Honourable Bill W. Diachuk, Minister responsible for Workers' Health, Safety and Compensation.

A cordial welcome is also extended to our hosts, the MEDICHEM CALGARY '83 ASSOCIATION and the representatives of government agencies, political parties, universities, trade unions and the media.

Nous souhaitons également la bienvenue aux délégués de la Province de Québec et d'autres parties du Canada francophone, et nous remercions vivement le Centre Canadien pour la Médecine de Travail et la Sécurité d'avoir prévu le service d'interprétations simultanées. Nous sommes convaincus que les communications scientifiques de nos collègues francophones contribueront essentiellement au succès de cette conférence.

Following MEDICHEM's 10th anniversary, which turned out to be a very successful event in Paris, we are starting into our association's second decade with this reunion held in this part of the globe again. The program has been prepared with commitment and enthusiasm, and with the intention of making this congress, too, a great success and a milestone in MEDICHEM's history. The scientific sessions have been excellently prepared, so we shall have the pleasure of listening to 4 review presentations and 4 invited presentations, and 36 papers will be discussed too. We are very grateful to Dr. Orford and Dr. Cowell, and all the other organizers behind the scenes for their support. They all have done a wonderful job. As it has become the custom during former conferences, I will say a few words on the present situation in the chemical industry.

It is MEDICHEM's policy to comply with occupational health, safety, and environmental protection measures required by law and relevent regulations. On the basis of our daily work, we are convinced that the chemical industry worldwide will always act with a great sense of responsibility whenever possible to prevent impairment of health, injuries, damage and loss involved in the production and use of chemicals. In order to minimize the problems, our association is always willing to cooperate with employers, employees, governments, local authorities, and academic and professional bodies. There is no doubt that it is one of MEDICHEM's strengths that we work internationally and thus provide a forum where occupational health problems in the chemical industry can be discussed worldwide. In order to achieve a full understanding of the occupational and toxicological problems, a close cooperation with the responsible authorities and agencies is essential. In 1982/1983 as well, our colleagues and the institutions and authorities have been exchanging views on current problems and on the implementation of laws and regulations. This willingness has owed much to MEDICHEMs initiative over more than 10 years to maintain regular contact and its policy of making available the more than 500 papers presented at its ten congresses voluntarily and early. It is also important that our members contribute to the MEDICHEM Newsletter and study the scientific literature so as to be always well informed on occupational health problems in the chemical industry.

I should like to express my thanks to all those who have contributed to the success of MEDICHEMs activities for the past ten years, to all our members, to our national representatives, to my colleagues on the Board, to the staff of the secretariats in The Hague, Malmö and Ludwigshafen, to the secretariats which have helped to organize a congress and last, but not least, to our wives.

For this congress the Board has chosen three themes:

- Occupational health and toxicological problems in the petroleum, gas and petrochemical industries

- Emergencies in the chemical industry: assessment and intervention, and

- Applications of computer technology in occupational health

A further important theme which is always on our agenda:

- Current occupational health problems in the chemical industry.

The Board hopes that the themes are acceptable and of interest to all our members. We should now listen and discuss them intensively and take the best solutions along with us.

It is especially appropriate that the first topic the identification and control of health hazards in the petroleum, gas and petrochemical industries will be dealt with here in Calgary, the oil and gas headquarters of Canada. We already know much, but - no doubt - never too much; therefore, we offer this subject in order to hear about new investigations and listen to papers, eg. on benzene, and provide data for necessary new conclusions from and recommendations for our daily work.

As to topic II "Emergencies", there is no "zero risk" on earth, although the chemical industry occupies one of the first places in both the industrialized and in many developing countries regarding safety in the workplace. The chemical industry is well aware of emergencies that could be caused by mechanical accidents, explosions, and intoxications by hazardous chemicals. Ready to take the responsibility, the chemical industry is prepared to respond to all these situations and to take the challenge very seriously. What is very important is the cooperative response by all departments of the company involved, such as the fire brigade, the security and safety departments and the medical department as well as close cooperation with local and national authorities.

Data collection and computerized analysis were chosen for discussion and theme III, because occupational health programs within industry have grown significantly and have become infinitely more complex in the last decade. As they are focused on the health implications of past, present and projected operations and products, the information must be handled efficiently and effectively.

A well-designed computerized health information system should allow for:

- standardized consistent record-keeping procedures and data collection
- a data base of continuous health and exposure information

on employees that will facilitate epidemiology studies
- support of administrative activities within the medical department on a day-to-day basis
- effective reporting system to evaluate potential problems,
- and enhancement of the response.

We know that around the world a number of companies have developed or are developing such systems on their own internal resources or have adopted commercially available systems. The American Occupational Association's Medical Information Systems Committee provides a sense of direction and possible sources of assistance to all those physicians in the chemical industry beginning a project in order to eliminate duplication and to highlight unique or innovative features. We hope that the papers published in the Journal of Occupational Medicine, Vol. 24, October 1982, and the papers of this congress will be a useful source and will stimulate further communication and advance the development of health information systems.

The success of an international congress depends primarily on its scientific value; however, the social side and the organization are important, too. Again this time, apart from an excellent scientific program, social events such as a visit to Glenbow Museum, a trip to Turner Valley and a barbecue, have been organized to acquaint us with the historic spirit of the magnificent city of Calgary. From a distance of 7,000 miles I learned that Calgary is the fastest growing city in the Canadian nation and its oil and gas headquarters, vibrant with life and energy. Therefore, let us enjoy our stay here where "the old west is captured and remembered", in the vicinity of the majestic Canadian rockies, in the company of old MEDICHEM friends, but let us also find time to look for and meet new ones.

Friendly encounters and mutual respect and esteem both in the scientific sphere and in personal human contacts have been MEDICHEM's strength right from the start, and it is my very sincere wish that this should remain characteristic of our international association in the future. Together, we shall meet all challenges successfully that are put to us no matter where we stand - be it at a university, in an institute, in government or in the chemical industry. Each one of us is called on to play his part.

Dr. Orford, as the General Organizer of this congress, please accept our MEDICHEM gavel in which the name Calgary has been engraved for 1983 in addition to the names of the other ten cities where the former congresses were held, for opening and closing the scientific sessions. We include in our cordial thanks Dr. Cowell's organizing and scientific committees and wish them very successful work so that all their endeavours are rewarded.

Wishing you "good luck", I declare the XIth MEDICHEM Conference open!

TECHNICAL REPORTS AND PAPERS

THEME I

OCCUPATIONAL HEALTH AND TOXICOLOGICAL PROBLEMS IN THE PETROLEUM, GAS, AND PETROCHEMICAL INDUSTRIES

HYGIENE PROFESSIONNELLE ET PROBLEMES DE TOXICOLOGIE DANS LES INDUSTRIES DU GAZ ET DU PETROLE ET DANS LES INDUSTRIES PETROCHIMIQUES

OCCUPATIONAL HEALTH AND TOXICOLOGICAL PROBLEMS IN THE PETROLEUM, GAS, AND PETROCHEMICAL INDUSTRIES

R. E. Eckardt
Scottsdale, Arizona, USA

I am not sure how many of you are aware of Dr. Julius Comroe's amusing and enlightening paperback book called "Retrospectroscope", with the subtitle "Insights into Medical Discovery". At one point in his book, he makes the following observation: "Science progresses by continuously revising, extending, or completely overturning existing "facts" to create new concepts that may become "facts" and in turn be revised or discarded; it rarely progresses by producing "breakthroughs" on demand" (1). After spending 30 years in the Petroleum-Gas-Petrochemical Industry, I can certainly testify to the fact that our knowledge progressed in a continuous manner, was frequently completely overturned as we learned more, and rarely was confronted with a "breakthrough". I guess the closest thing to a "breakthrough" that occurred in those 30 years was the demonstration that vinyl chloride could cause angiosarcoma of the liver in both humans and animals. Rather than a breakthrough, however, I think vinyl chloride could be better described as a bombshell. I know of no other event that made such a lasting impression on management as this one did. As a result, the Chemical Industry Institute of Toxicology (CIIT) was created, and many corporations either enlarged existing toxicological facilities or started toxicology programs of their own when they previously did not have any such program.

Additionally, many corporations which did not have a Medical Director arranged to hire one, much impetus was given to epidemiological studies, and computerization of medical, toxicological and industrial hygiene data was greatly stimulated. So in a way, this discovery may have served as a boon to worker health rather than the catastrophe it was originally thought to be.

In many people's minds, the present is an era of the exotic diseases - carcinogenesis, mutagenesis, congenital defects, reproductive toxicology, behavioral toxicology, neurotoxicity and so forth. For a few moments I would like to remind everyone here that such exotic diseases may not be the most important in terms of total illness or disability of the work force. In January of this year, the U.S. National Institute of Occupational Safety and Health (NIOSH) published a list of the ten leading work-related diseases and injuries (2). Number one on the list was occupational lung diseases which included asbestosis, byssinosis, silicosis, coal workers' pneumoconiosis, lung cancer, and occupational asthma. With the exception of byssinosis, every one of these may be found in the petroleum, gas and petrochemical industries. Exposures to asbestos may occur when asbestos-containing insulation is ripped off piping during repair or rebuilding work. Some petroleum-related industries have even gone as far as recommending that asbestos insulation be banned and non-asbestos containing insulation be substituted for asbestos-containing insulation, so that hopefully in time this hazard may be eliminated. However, this may take years to accomplish, so we should not lightly dismiss it. Silicosis can occur among sandblasters and sandblasters' helpers when equipment is being cleaned up during repairs. Many petroleum companies have acquired vast coal holdings, some of which are being operated as coal mines, and others for research on converting coal to liquid products. Many dusts and catalysts may be found in petroleum-related industries and contribute to cases of occupational asthma, and, of course, the previously mentioned asbestos may contribute to lung cancer or mesothelioma. Thus this list of occupational lung diseases cannot be ignored in the petroleum, gas and petrochemical industries. In order to keep this presentation short, I will use the term petroleum-related industries to replace the petroleum, gas and petrochemical industries.

The second item on NIOSH's list is musculoskeletal injuries, including back, trunk, upper extremity, neck, lower extremity and traumatically induced Reynaud's phenomenom. I will not further elaborate on this since I think any physician from a petroleum-related and most non-petroleum related industries has seen many of these. In fact, in many industries the safety departments devote much of their time in trying to teach proper work procedures so that these injuries may be avoided or minimized. Traumatically induced Reynaud's phenomenom, from the use of vibrating tools has recently been the subject of special conferences designed to find solutions to it. Whether these conferences have achieved their objectives only time will tell. In fact, NIOSH has recently completed a comprehensive study of this condition and has issued Current Intelligence Bulletin #38. Vibration Syndrome (Publication No. 83-110), March 29, 1983 (3).

Number three on the list is occupational cancers (other than lung) including leukemia, mesothelioma, and cancers of the bladder nose and liver. Again, I will not elaborate on this list because I think we are all aware of the presence of carcinogens in petroleum-related industries from benzene, at one end of the molecular scale, to polynuclear aromatic hydrocarbons at the other. Further, I intend to address this later in greater detail.

Number four on this list is amputations, fractures, eye loss, lacerations and traumatic deaths. Again, I think this list needs no elaboration except one. Baker and colleagues (4) undertook an epidemiological study of all 148 fatal work-related injuries in the state of Maryland. They found the leading cause of death was motor vehicle accidents of many kinds and the second leading cause was assault with guns. In fact, road vehicles accounted for 25% of the deaths, with non-road vehicles contributing another 16% for a grand total of 41%. Firearms accounted for an additional 11%. Interestingly, in 11% of the workers tested, blood alcohol concentrations were 0.08% by weight or greater.

In commenting on this paper editorially, Omenn (5) pointed out that in Morbidity/Mortality weekly reports (MMWR) tables (6) showing "potential years of life lost before age 65", accidents take the greatest toll, totalling 27% of the total. Further, he pointed out that these tables show that accidents plus homicides and suicides cost more years of life than malignant neoplasms and heart disease combined. It is statistics like these that certainly must give us pause when we are examining our priorities. It has always seemed to me that the occupational physician, although his primary concern should be with occupationally caused deaths, injuries, and illnesses, must not lose sight of other causes. This has been supported by many major corporations who have begun programs to make their employees as safety conscious at home as they are on the job. They have found that such programs are really worthwhile because they have significantly reduced off-job losing time accidents. This program was originally started by the Dow Chemical Co. who spread the word about its effectiveness and in this way encouraged other corporations to adopt it.

Fifth on the list is cardiovascular diseases including hypertension, coronary artery disease and acute myocardial infarction. With all the attention being given in the lay press to stress and burnout, the physician certainly cannot ignore a possible relation between them and these cardiovascular diseases. In fact, in New Jersey just before I retired, a second coronary occlusion occurring on the job was presumed to be job stress-related for compensation purposes.

Number 6 on the list is Disorders of Reproduction including infertility, spontaneous abortion, and teratogenesis. I will have more to say on this later on.

Seventh on the list is neurotoxic disorders including peripheral neuropathy, toxic encephalitis, psychoses and extreme personality changes (exposure-related). This is an area about which I will speak more on later, but one which, except for peripheral neuropathy and a few well-recognized severe personality changes (as from mercury or methyl bromide) needs much more research, including epidemiological studies, before the various causes completely sort themselves out.

Number 8 on the list is noise-induced loss of hearing. Again, there has been so much said on this in the literature that my only further comment on it is that a hearing conservation program needs to be carefully designed and performed, and needs the cooperative efforts of the physician, the industrial hygienist, and the otologist, all operating with well designed testing facilities. In a recent article, Sataloff and Sataloff (7) emphasized that ensuring ear protectors are properly worn is an important part of an effective hearing conservation program. This requires employee education, periodic audiometric testing, looking for temporary threshold shift, additional counselling, and, if necessary, disciplinary action.

Ninth on the list is dermatologic conditions, in which dermatoses, burns (scaldings), chemical burns and contusions (abrasions) are all included. I am sure that any physician in a petroleum-related industry has had to deal with all of these. Dermatoses will be seen not only among his own employees, but also among customers and users of his products. In a study done years ago for the American Petroleum Institute at the then Industrial Hygiene Foundation (now the Industrial Health Foundation) it was concluded that over 60% of all dermatoses and 12% of all occupational diseases were the result of contact with petroleum products. This study was done so many years ago that I am unable to produce a reference to it for you, although I think it was published in the Archives of Industrial Health or one of its predecessor journals. In any event, it led to a program sponsored by the American Petroleum Institute and some individual companies stressing preventive measures for those who use petroleum products regularly.

Finally, number 10 on the list is psychologic disorders such as neuroses, personality disorders, alcoholism, and drug dependency. I presume NIOSH intended to distinguish between item 7 on the list and item 10 on the basis that item 7 diagnoses were the result of over-exposure to toxic materials at work, while item 10 diagnoses were precipitated by psychological stresses at work. In any event, as I have indicated under item 7, I think this whole area is one which is going to require much more research before we can conclude that some of these conditions are work-related. Basically, however, I have no quarrel with NIOSH's list of ten, although as previously implied, there are situations where I think there are legitimate grounds for disagreement. It is this area of disagreement that I would like now to discuss in some further detail.

I would like to begin with benzene and its relationship to leukemia. That benzene is leukemogenic under certain circumstances of exposure was even recognized by me (8) as long ago as 1959. At that time the general thinking was that leukemia occurred in people who had suffered a rather severe depression of their bone marrow as a result of rather severe exposures to benzene. If they did not die as a result of aplastic anemia, they were nonetheless subject to the later development of a fatal leukemia. When Infante and co-workers (9) published their first epidemiologic studies suggesting that leukemia could result from exposure levels that had never produced any bone marrow depression, a great deal of skepticism about the validity of their observations was expressed. Even though these observations were reputed to be confirmed and enlarged upon (1), this skepticism has persisted. More recently, Maltoni and associates (11) have proposed that benzene produces more malignancies than just leukemia. They claim that benzene produces, in rats, zymbal gland carcinomas, carcinomas of the oral cavity, hepatocarcinomas and possibly mammary carcinomas. However, their data have not been subject to careful statistical analysis, so it is not clear whether all of the claimed results of benzene can be accepted at face value. In fact, in commenting on the Maltoni et al. data, Goldstein (12) severely criticizes the relevance of their observations to the human situation. For instance, he points out, zymbal gland tumors have no counterpart in the human, carcinomas of the oral cavity only occurred in animals that were gavaged, not in those inhaling benzene, and multiple previous experiments with benzene had never suggested that it was a hepatocarcinogen. He concludes that a great deal more research, especially on basic mechanisms of action, will be necessary before we fully understand the relationship of benzene to leukemia. This is a conclusion which I heartily endorse, and hope that regulators have the sense to comprehend this before making regulations that might wreak economic havoc to a multitude of industries. Benzene is so ubiquitous, being found in measurable quantities in ambient air, that we must make haste in this field with caution and thorough understanding. This does not mean that irresponsible exposures to benzene should be permitted. Exposures should be kept to as reasonably low a level as possible, certainly not in excess of 10 ppm, and preferably even to lower levels where this is feasible.

TABLE 1: The Ten Leading Work-Related Diseases and Injuries - United States, 1982*

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1. Occupational lung diseases:
   asbestosis, byssinosis, silicosis, coal workers' pneumoconiosis, lung cancer, occupational asthma

2. Musculoskeletal injuries:
   disorders of the back, trunk, upper extremity, neck, lower extremity; traumatically induced Raynaud's phenomenon

3. Occupational cancers (other than lung):
leukemia; mesothelioma; cancers of the bladder, nose and liver

4. Amputations, fractures, eye loss, lacerations, and traumatic deaths

5. Cardiovascular diseases:
hypertension, coronary artery disease, acute myocardial infarction

6. Disorders of reproduction:
infertility, spontaneous abortion, teratogenesis

7. Neurotoxic disorders:
peripheral neuropathy, toxic encephalitis, psychoses, extreme personality changes

8. Noise-induced loss of hearing

9. Dermatologic conditions:
dermatoses, burns (scaldings), chemical burns, contusions (abrasions)

10. Psychologic disorders:
neuroses, personality disorders, alcoholism, drug dependency

*The conditions listed under each category are to be viewed as selected examples, not comprehensive definitions of the category.

The next item I would like to discuss is brain tumors in the chemical industry, particularly the petrochemical industry. As most of you are probably aware, the New York Academy of Sciences held a symposium on this topic from October 27 to 29, 1980. The Proceedings of that symposium were published on April 30, 1982 (13). These Proceedings make very interesting, if somewhat confusing reading from two standpoints. First, there is a considerable amount of conflicting epidemiological data. It must be admitted that much of this epidemiological data was preliminary, and crude, so that about the best that one could conclude was that decisions would have to await more studies. The second interesting thing about these Proceedings is that practically all participants agreed that if there is an increased incidence of brain tumors in the petrochemical industry, no one had a good idea of what the causative agent might be. Obviously there are carcinogens in the petrochemical industry, but a superficial review of the cases that had occurred did not suggest a common exposure. At this workshop or symposium, a somewhat unique situation was pointed out in that industry and government would work cooperatively as a team in studying the problem at least in the Union Carbide data. Unfortunately, it did not seem to work out that way.

In April of this year, Austin and Schnatter (14) analyzed the Union Carbide data in some detail. They found a small excess of brain cancer deaths but concluded there was insufficient evidence to conclude that these tumors were occupationally related. In an accompanying paper (15) they could find no common exposure in those brain cancer cases they did observe, which they believe is further support for the concept that these cancers are not occupationally related. Previously, Waxweiler and Associates (16) had reported on the same cases, and had made the very weak conclusion that "although non-occupational etiologies cannot be dismissed, these data suggest an occupational etiology for certain brain tumor deaths in petrochemical workers". In comparing the Austin and Schnatter paper with the one by Waxweiler et al., it is interesting that Austin and Schnatter excluded meningiomas from their analysis while Waxweiler et al. did not. Also, Austin and Schnatter excluded two workers who had worked for so short a time that it would be unlikely that their brain tumors were occupationally related. These were not excluded by Waxweiler et al. Finally, Austin and Schnatter excluded a case that a panel of pathologists at the Armed Forces Institute of Pathology said was not a brain tumor. It is not clear whether Waxweiler et al. did exclude this case or not. In any event, Austin and Schnatter ended up with 10 accepted cases, whereas Waxweiler et al. had 19 cases. In addition, Waxweiler et al. extended the time of the study apparently arbitrarily, even though presumably the time limits for the study had been agreed upon beforehand. Thus, this so-called cooperative industry-government study ended up as two separate analyses using different data bases and reaching different conclusions. It is not my intent to try to say who is right and who is wrong in this situation. The point I do wish to make, however, is that this situation still remains unsettled and will require additional intensive study before we can be assured just what the situation is. Two additional studies that have been reported (17,18) from Dow Chemical Company do not do much to alleviate this dilemma. The latter study (18) was a joint industry-government analysis. It thus seems to me that at this point in time we do not have a final answer on brain tumors in the chemical and/or petrochemical industry but will have to await further studies which will give us definitive answers. The problem is so important that it is to be hoped that such studies will be continued and intensified.

Perhaps some of you may have read in your local newspapers that the American Petroleum Institute had suggested that gasoline stations might wish to consider labelling their gasoline pumps as containing a potential carcinogen.

Another group that is of interest and hopefully can be followed are the gasoline sniffers. Incidentally, sniffing various materials to get a high on, is not new to our generation or century. Comroe (19) points out that as long ago as 1842 people used to hold ether or nitrous oxide sniffing parties as a lark.

Hexane as a cause of peripheral neuropathy came also as a bit of a surprise. It was given added importance when methyl normal butyl ketone was discovered to produce a similar neuropathy (20). Actually, hexane as a neurotoxin had been reported at the meeting of the PCIAOH in Tokyo and recommendations for the lowering of the threshold limit value (TLV) were made (see Proceedings of XIXth International Congress on Occupational Health). In some neat metabolic studies, Divincenzo and Associates (21) showed that a common pathway through 2,5-hexanedione accounted for both the neurotoxicity of hexane and methyl-n-butyl ketone. Subsequently it has been shown that a n-hexane "free" hexane mixture (for instance, methyl pentane) (22) does not produce a peripheral neuropathy because the formation of 2,5-hexanedione is blocked. This whole situation is one which has led to a great deal of metabolic studies, which have been of great interest.

Finally, Lynch et al. (23) reported an association of upper respiratory cancer with exposure to diethyl sulfate. It had been known since 1952 (24) that upper respiratory cancers occurred in isopropyl alcohol manufacture. It remained for Druckrey and Associates (25) to demonstrate that dialkyl sulfates were highly carcinogenic in rats. It was Lynch et al. thinking that when strong sulfuric acid was used in either ethanol or isopropanol manufacture that large quantities of diethyl and diisopropyl sulfates, respectively, were formed. Now that weak sulfuric acid is used in these processes, it is believed that insignificant quantities of the dialkyl sulfates are formed, and that therefore the problem no longer exists. However, a 1976 report (26) suggested that there might be an increased incidence of cancer in a Shell Co. weak acid isopropanol plant. This observation, if confirmed, would throw some doubt on the weak acid vs. strong acid theory. To date, I have not seen any confirmation of the Lynch et al. report or the anonymous report of Shell's findings. Again, therefore, it will be necessary to await additional studies and reports before we have the final answer.

I think it is most important that we keep an open mind about NIOSH's item 10, namely, psychologic disorders. Whether, for instance, alcoholism can be considered as work-related, except perhaps in salesmen who indulge in the 3 martini lunch, seems highly questionable to me. I don't mean to imply that alcoholism should not be of concern to the occupational health team. Some anti-alcoholism programs instituted in industry have been highly successful, and have resulted in the salvage of many valuable workers. For this reason, whether it is work-related or not may be a moot question. I think the same comments should apply to the other 3 subheadings - neuroses, personality disorders, and drug dependence.

The question of reproductive toxicology is relatively new. I think for us to maintain credibility in this area, we must develop well thought out and well conducted studies. Hanis and Phillips (27) have recently discussed the development of such a program for one company. They stressed that to be successful any such program must have a high degree of acceptability among workers and management. They proposed that 4 types of data need to be collected. The first three consist of 1) demographics and identifiers; 2) reproductive history; 3) risk factors or confounders related to reproductive outcome. These 3 may be obtained by questionnaires and/or interviews with workers and spouses. The final sets of data on reproductive outcome are more difficult to obtain and validate. They include pregnancies, fetal deaths, sex of offspring, birth weights and live births.

Finally, I would like to close this brief review with a consideration of some philosophical aspects. It seems today that we live in an adversarial and litigious world. Over the past 3 years, 2 prominent members of the Permanent Commission and one prominent U.S. industrial hygiene elder have addressed some of these problems. First, Dr. Rene Truhaut (28) in the 1980 Yant Memorial Lecture spoke on "The Problems of Thresholds for Chemical Carcinogens - its importance in industrial hygiene, especially in the field of permissible limits for occupational exposure". He made a strong plea that we be intelligent and reasonable in the interpretation of scientific facts, especially where such exposures are inevitable, as with polynuclear aromatic hydrocarbons and aflatoxins. The next year, 1981, Dr. Ernest Mastromatteo (29) entitled the Herbert E. Stokinger Lecture "On the Concept of Threshold". Even insofar as carcinogens are concerned, he endorsed the plea of Dr. Truhaut the preceding year. Finally, the 1982 Herbert E. Stokinger Lecture by Hervey B. Elkins (30) was entitled "The real world - or science fiction". Dr. Elkins ridicules some of the estimates of excess deaths from environmental or occupational exposures that have been made. He believes such estimates are so far out of line because their proposers cannot or will not accept the concept of a TLV. In essence, he supports and reinforces what Drs. Truhaut and Mastromatteo had already stated. None of these distinguished men have ever been known to be excusers for industry. Their remarks coming on consecutive years to the national meeting of the American Industrial Hygiene Association are recommended to you strongly as required reading.

In this brief talk, I have attempted to show that the petroleum, gas, and petrochemical industries have health problems that are not unique to these industries, but are present in all major industries. They also have some health problems which are relatively unique to themselves. Some of these are well established, whereas with others there still remains considerable controversy on their validity. These questions need to be addressed and answered honestly and without prejudice, either by industry, government, or labor. Finally, I have tried to present to you the thinking of 3 distinguished scientists who all believe that the concept of TLV's is essential if we are to do the maximum job in protecting both workers' health and their jobs.

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RENAL TOXICITY AND CARCINOGENICITY OF PETROLEUM HYDROCARBONS IN RATS: A CRITICAL ANALYSIS

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The clinical evidence

Exposure to solvents has been regarded as a cause of human kidney disease for more than 20 years. Concern about renal tubular disease in man caused by excessive exposure to solvents or solvent mixtures (Allen, 1962; Heptinstall, 1974) was followed by reports that volatile hydrocarbons could induce glomerular disease manifesting itself as Goodpasture's syndrome, with proliferative and extracapillary glomerulonephritis (Beirne and Brennan, 1972; Zimmerman et al., 1975). The name "membranous nephropathy" was applied to such cases of autoimmune glomerulonephritis on the theory that antibody production followed solvent-induced injury of lung or kidney membranes (Ehrenreich and Churg, 1968; Ehrenreich et al., 1977).

To apply these and related reports (Lagrue et al., 1977; Ravnskov et al., 1979) to an assessment of human hydrocarbon exposure one has to discriminate much more fastidiously between what have loosely been termed 'hydrocarbons' and the varied assortment of solvents--for the most part chlorinated aliphatic and aromatic compounds--claimed to have been involved in one or other of the published cases of membranous nephropathy. Phillips (1983) has reviewed the literature and reached the conclusion that massive exposure to petroleum distillates may, rarely, cause tubular necrosis that results in acute renal failure, a reversible condition that has no long-term consequences. Mild degrees of presumably reversible tubular damage have been reported (Mutti et al., 1981; Franchini et al., 1983) in workers exposed to a mixture of aliphatic and alicyclic C_5-C_7 hydrocarbons at levels mostly exceeding the TLV. However, no firm foundation exists for an association between occupational exposure to hydrocarbons and glomerulonephritis (Churchill et al. 1983).

Evidence of animal experiments

To what extent are studies in animals capable of predicting or supporting the effects claimed to have been observed in man? If one considers the results of immunological studies on rats and mice exposed by inhalation to vapors of unleaded gasoline (PA-6 study described below), attempts to locate glomerular basement membrane antibodies in kidney and lung yielded negative results (Kuna, 1981; MacFarland, 1983).

What has emerged very clearly in recent years is a characteristic picture of rat nephropathy, mainly in males, in response to exposure to a variety of petroleum hydrocarbon fractions (Scala, 1982). The initial 90-day rat and mouse studies have now been extended to encompass approximately 2 years of inhalation exposure to unleaded motor gasoline (Table 1). Among non-neoplastic lesions, a distinctive new feature--mineralization of the renal papilla--has been recognized (Busey, 1983; Cockrell et al., 1983; MacFarland, 1982). Besides serving to define more clearly the time relationship of the various elements in rat hydrocarbon nephropathy (Table 2), the long-term PS-6 study has revealed the development of renal neoplasia, which is discussed below (MacFarland 1982, 1983)

TABLE 1: API Gasoline Inhalation Studies in Fischer 344 Rats and B6C3F1 Mice

Duration	Lead content of gasoline (mg/gallon)	Levels of exposure[a] (ppm)
90 days	Unleaded: 5 Leaded: 1940	383, 1552 103, 374
2 years[b]	Unleaded PS-6 (2% benzene)	67, 292, 2056

[a] 6 hr/day, 5 days/week; total volatilization
[b] Actual duration 24-26 months; interim sacrifices at 3, 6, 12 and 18 months.

TABLE 2: Early Focal Lesions in Male Rats Forming Part of the Characteristic Hydrocarbon Nephropathy

0 Hyaline droplet formation

0 Degeneration and regeneration of proximal convoluted tubules

0 Tubular dilatation and cellular necrosis at the CMJ

0 Karyomegaly and associated changes in the pars recta

[a] CMJ - Corticomedullary junction

The early lesions of rat hydrocarbon nephropathy consist of scattered foci, with 5-10% of the kidney affected in males only. The beginnings of the progressive renal tubular disease are apparent at 3 months, even at levels as low as 67 ppm gasoline, concomitantly with an increase in relative kidney weight. The lesion that has proved most important, because it is so readily identified at the light-microscope level, has been tubular dilatation and necrosis, occurring at the corticomedullary junction (CMJ). It is also the best dose-response indicator because, unlike hyaline droplet formation and the foci of degenerating/regenerating proximal convoluted tubule cells in the cortex, there is not a background incidence to contend with. The lumen in most of the tubules is filled with granular proteinaceous material, most probably cellular debris, while the surrounding epithelial cells are necrotic, with pyknotic nuclei (Halder et al., 1983; Busey, 1983; Cockrell et al. 1983).

Scattered foci of degenerating and regenerating cells of the proximal convoluted tubules are seen in the cortex, the former characterized by increased eosinophilia and the latter by increased basophilia. The regenerative hyperplasia of the epithelial lining cells is a further landmark of rat hydrocarbon nephropathy. According to Halder et al. (1983), a chronic inflammatory process, marked by interstitial mononuclear cell infiltration, is associated with the lesions in the cortical tubules.

It is tempting to attribute tubular dilatation to back pressure caused by the mass of cellular debris carried down within the nephron from the necrotic proximal convoluted tubules, in relation to the natural constriction that exists between the S_3 segment of the pars recta and the thin descending limb of the loop of Henle. Nevertheless, at the moment this interrelationship is speculative. It is supported by observations of angular lysosomal structures in cells of the tubules of the S_3 segment, suggestive of uptake of cellular debris. On the other hand, it is this segment of the pars recta that is affected by numerous nephrotoxins, including hexachloro-1,3-butadiene (Berndt, 1983; Ishmael et al., 1982; Wolf et al., 1983). There is evidence that the cells of the S_3 segment are highly active metabolically, so that conversion of nephrotoxic hydrocarbon moieties to chemically reactive metabolites could occur locally. Alternatively, differential destruction of cytochrome P-450-dependent monooxygenases at this site by the nephrotoxic agent may account for species and sex specificity (Wolf et al., 1983).

The early appearance of hyaline droplets in the epithelial cells of the proximal convoluted tubules is indicative either of excessive production (in the liver) of α_{2u}-globulin, characteristic physiological protein present in the urine of the male rat, or of impairment of the normal excretion of this protein (Neuhaus et al., 1981). Our knowledge of α_{2u}-globulin has been advanced by the work of Vandoren et al. (1983), who have demonstrated the microheterogeneity of the protein, the fact that different forms are synthesized by female rats (in the submaxillary gland as well as the liver), and are present in the blood and urine--albeit in far smaller amounts than in males. But what the relationship is, if any, of heavy hyaline droplet formation to the other pathological changes seen in the kidney following hydrocarbon exposure remains a mystery.

The last of the non-neoplastic effects to appear is papillary mineralization, clearly distinguishable from the random, sporadic calcification of renal tubules that occurs in old rat nephropathy (Gray et al. 1974; Gray, 1977; Harwood, 1982). Papillary mineralization was seen at 12 and 18 months in groups exposed to 2056 and 292 ppm gasoline.

Karyomegaly was a feature of the cells of the pars recta situated in the outer stripe of the medulla. It was apparent within 2 months and was later associated with hyperplasia and abundant mitoses, thus perhaps paving the way for the development of carcinoma in situ and the renal tumors, which were found predominantly in the pars recta (Trump, 1983). This view of karyomegalic changes as preneoplastic events is an interesting link to similar effects which are the hall-marks of the renal toxicity of lysinoalanine in rats (Woodard and Short, 1977). The significance of this observation is discussed below.

Categories of active components

Clearly, the induction of rat nephropathy by hydrocarbons does not result in a completely uniform pattern of pathological changes. A fully consistent relationship between chemical structure and biological activity is by no means clearly discernible; but the existence of considerable differences in potency is indisputable.

In the case of the gasoline studies sponsored by the American Petroleum Institute (Table 1), the detailed composition of the PS-6 motor gasoline is summarized in Table 3. Past experiments, and more recent studies, demonstrating nephrotoxicity of various hydrocarbons in rats have been brought together in Tables 4 and 5. No claim for completeness of this information can be made with respect to a field that is developing so rapidly. Nevertheless the prominence of isoparaffinic fractions among the biologically active materials is noteworthy. By contrast, predominantly aromatic fractions tend to be inactive.

In a series of 21-day inhalation studies in rats with five different naphthas and an unleaded gasoline blend (Halder et al., 1983) the results were all positive to varying degrees, except only for heavy catalytic reformed naphtha (93% aromatics, 7% paraffins), which was not nephrotoxic. The API screening program has yielded a number of other negative results, particularly with solvents of high aromatic content. Interestingly, Easley et al. (1982) reported renal toxicity in mice, especially females, exposed by dermal application to middle distillates of shale oil and petroleum (JP-5, JP-8 and diesel fuel marine). They considered the etiology to be vascular, mediated through chronic ischemia. The PS-6 studies to which reference was made above revealed no such effect.

TABLE 3: Composition of PS-6 Motor Gasoline[a]

Generic Stream[b]	Volume %	Analytic data			Volume
		Fraction	C_x through	C_y	
LCCN	7.6	n-Paraffins	3	10	11.4
HCCN	44.5	Isoparaffins	4	13	46.5
LCRN	21.3	Cycloparaffins	5	13	4.7
LAN	22.0	Monoolefins	2	12	9.0
Benzene[c]	0.8	Aromatics	6	13	28.4
Butane	3.8				

[a] R. W. King (1982). Report to W. G. Domask

[b] Streams: LCCN, HCCN--light and heavy catalytic cracked naphthas; LCRN--light catalytic reformed naphtha; LAN--light alkylate naphtha

[c] Total benzene content 2%

While most of the definitive studies in recent years have involved exposure of experimental animals by inhalation, it has become obvious that a more rapid and flexible mode of administration was essential for progress to be made in screening the vast number of streams, fractions and products in the field of solvents and fuels. Administration by gavage has been developed as an acceptable alternative to inhalation for screening purposes (Bogo et al.1982).

Hydrocarbon oncogenesis in the rat kidney

In comparison with the typical effect of renal carcinogens (Hamilton, 1975), hydrocarbon oncogenesis is characterized by the long latency and low yield of the resulting renal tumors.

From the eighteenth month to the end of the PS-6 study, renal neoplasia supervened; with one exception the tumors occurred entirely in male rats (Table 6). The primary renal neoplasms were situated in the cortex, or near the renal poles, predominantly in the pars rectae. The tumors were microscopic in size, hence not visible grossly, and were unlikely to be the cause of death (MacFarland, 1982). They did not metastasize. One renal sarcoma was found in a female rat at the 18-month sacrifice. From Table 6 it is clear that the incidence of renal neoplasms was dose-related.

TABLE 4: Male Rat Nephropathy Produced by Hydrocarbon Solvents

Solvent	Composition (%) AR	P	N[a]	References
60 Solvent	27	50	21	Carpenter et al. (1975a, b, 1977)
Stoddard	14	48	38	
High naphthenic	1	29	70	
VM&P naphtha	12	55	33	Lione (1981), cited by Scala (1982)
Naphthenic-Ar	38	25	37	
70 Solvent	16	58	26	
A	0.02	99.9	0.1	Kuna and Ulrich (1982), cited by Scala (1982)
B	0.03	99.9	0.1	
C	0	52	48	
D	21	55	24	
Decalin				Alden et al. (1982)
C_{10}-C_{11} Isoparaffinic				Phillips and Egan (1983 a,b); Phillips and Cockrell (1982) Cockrell et al. (1983)

[a] Ar--aromatics; P--paraffins; N--naphthenes

TABLE 5: Male Rat Nephropathy Produced by Hydrocarbon Fuels

JP-4	McNaughton and Uddin (1983) (McN-U)
JP-5 (petroleum or shale), diesel fuel marine	Parker et al., (1981); Cowan and Jenkins (1981); Gaworski et al., (1982); Bruner (1983); NcN-U.
JP-5 (petroleum distillate fraction)	Bogo et al. (1982); Pitts et al. (1983)
JP-7,8,TS	McN-U
JP-10 (cyclic aliphatic hydrocarbons)	Bruner (1983); McN-U
RJ-5 (synthetic fuel)	Bruner (1983); McN-U
Pentane, branched chain isomers	Pitts et al. (1983)

TABLE 6: PS-6 Study: Primary Renal Neoplasms in Male Rats

Group	Level of exposure (ppm)	Types of neoplasms			Total tumors
		Adenoma	Carcinoma	Sarcoma	
I	0	0	0	0	0
II	67	0	2	0	2
III	292	2	2	1[a]	5
IV	2056	1	6	0	7

[a] One sarcoma of the kidney occurred in a female rat

In addition to unleaded gasoline, synthetic fuels JP-10 and RJ-5 have yielded renal cell tumors after exposure of male rats, to levels of 556 mg/m^3 and 150 mg/m^3 respectively, for 6 hr/day, 5 days/week over a period of 1 year, followed by lifetime oncogenic observation. Under these conditions JP-10 [exo-tetrahydrodi-(cyclopentadiene)] and RJ-5 [endo-endo-dihydrodi-(norbornadiene)] yielded substantial numbers of primary renal cell tumors (Bruner, 1983).

In comparing the antecedent events in rats with those in human renal carcinogenesis, one finds considerable differences. Whether or not 'old rat nephropathy' plays a role in the development of renal neoplasia, spontaneous or otherwise, it is certainly a pathological feature that is strikingly different from aging changes in the human kidneys (Trump et al., 1983) or in organs with interstitial lesions and fibrosis. The exception is the association of renal adenocarcinoma with chronic renal disease in patients undergoing chronic dialysis (Hughson et al., 1980).

Oncogenesis in a second species?

In unexposed mice of the PS-6 study, the incidence of spontaneous liver tumors was 45% in males and substantially the same in gasoline-exposed males. In female controls the incidence was 14%, rising to 48% at the highest level of gasoline exposure. The latter is a statistically significant response, but biologically it may be indicative of a potent promoting action. The fact that gasoline is an inducer of mixed-function oxidase activity in rats and men (Harman et al., 1981) and that the dermal application of crude oil to the skin of rats selectively but powerfully induces such enzyme activities (Rahimtula et al., 1982) makes it likely that an analogous effect had occurred in mice exposed to gasoline. Enzyme inducers of this sort can exercise effective promotion in the mouse, leading to substantially increased liver neoplasia (Peraino et al., 1973; Uchida and Kirono, 1979; ECETOC, 1982). The increase in relative liver weight in exposed female mice supports this suggestion.

The Analogy of lysinoalanine and other nephrotoxins

The production of renal cancer in rats by motor gasoline focuses attention on the pathogenesis of the initial nephropathy and the question of a relationship, if any, between the early lesions and the late development of neoplasia. Elucidation of the biochemical and functional basis of the early effects is an essential element in developing an understanding of mechanism, and hence of significance to man. It is easier to lay out an agenda of questions that demand answers by means of further research than to grapple with the issue of interpretation.

Nevertheless, some guidance may be forthcoming from the analogy with lysinoalanine (LAL), a common component of food that is cooked or otherwise processed. LAL is consumed in appreciable quantities every day by the human population (Sternberg and Kim, 1977). As mentioned above, LAL produces nephrocytomegaly in the rat (Arnaud et al., 1977; Finot et al., 1977) and a pathological picture that is not unlike the renal lesions elicited by petroleum hydrocarbons (Woodard and Short, 1977; Gould and MacGregor, 1977). Tests of LAL in other species (dog, mouse, hamster, Japanese quail and monkey) at much higher doses have not elicited nephrotoxicity (de Groot et al., 1976; Anonymous, 1976). In this instance the source of rat nephrotoxicity, and the basis for the species specificity, have been traced to the uniquely high activity of rat kidney L-amino acid oxidase. This enzyme converts LAL to 1,7-diazabicyclo[4:3:0] nonane 6,8-dicarboxylic acid (Leegwater, 1978). After treatment with LAL, this cyclization product is present in urine of rats but not of hamsters (Leegwater, 1978). The cyclization product is proposed as the responsible agent that brings about the cytomegalic alterations in the lining cells of the pars rectae of the rat kidney, thus accounting for the unique nephrotoxic effects of LAL in this species.

On a quantitative basis, the widespread occurrence of LAL in processed foods (Sternberg and Kim, 1977) means that, where such foods do not constitute a major proportion of the diet, the total daily intake does not attain the levels necessary to induce karyomegaly in the rat. Gould and MacGregor (1977) have pointed out that the relatively high LAL levels (200-600 ppm) in certain infant formulas may present a risk to infants subsisting entirely on them. There is, however, no evidence for nephrotoxicity of LAL in man.

Notable among the many other chemical agents that induce renal cortical tumors in rats and mice are inorganic lead salts. The doses used for this purpose far exceed those that could be tolerated by man. There is no evidence that human exposure to lead causes cancer of any sort, nor even that it predisposes to the development of human neoplasia (Hamilton, 1975).

Essential steps towards interpretation

Whether or not the effects of such rat nephrotoxins are comparable with hydrocarbon nephropathy, the examples cited indicate the approaches that are essential to provide a basis for hazard assessment in man. The active hydrocarbon fractions appear to be virtually devoid of genotoxic actively (Conaway et al., 1982; MacGregor et al., 1982). Obviously, human epidemiology has a notable contribution to make towards the solution of this problem. But the comparison of the male rat with the female, and with other species, including man, has to be made on a systematic basis through an understanding of the mechanism by which nephrotoxicity develops. The use of individual active compounds, such as decalin, that elicit rat nephropathy, should lead to a clarification of the biochemical basis of its effects and the reasons(s) why female rats and animals of other species are unaffected. Simultaneously, the sequence of pathogenesis should be elucidated, trying to determine with all available sophisticated approaches the relationship, if any, between the nephropathy and the renal cancer.

There is, in the making, a new and notable chapter in the history of what the late Horace Gerarde (1961) called "the ubiquitous hydrocarbons". I fully anticipate a quantum leap forward in knowledge of both the toxicology of petroleum and synfuel hydrocarbons, as well as the pathogenesis of rat kidney toxicity and cancer. The new information will undoubtedly benefit workers, industry and the general public.

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AN EVALUATION OF POSSIBLE EFFECTS ON HEALTH FOLLOWING EXPOSURE TO ETHYLENE OXIDE

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Abstract

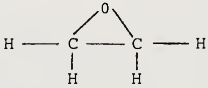
A study was made of the effects of ethylene oxide (ETO) on the health of sterilizer workers and other personnel exposed while using the agent for the sterilization of disposable medical devices. The only significant findings were obtained by chromosomal analysis of cultured lymphocytes harvested from the workers. There were significant differences in the numbers and types of chromosomal aberrations between the exposed workers and the non-exposed controls. Quadriradial and triradial chromosomic forms which are rarely found in non-exposed populations were increased in exposed workers. Increased numbers of sister-chromatid exchanges were found in the cultered lymphocytes of some, but not all, exposed persons. When the number and types of chromosomal abnormalities found among the exposed group were compared to values obtained from other measurements, no significant correlations were found between the following matches: values obtained in the blood chemistry profile, number and type of white cells, age of the employee, smoking history, years of exposure and sperm counts. Recommendations are made for continuing medical surveillance of persons working with ETO, based on this experience.

Résumé

Une étude a été entreprise concernant les effets de l'oxyde d'éthylène sur la santé des travailleurs de la stérilisation et autre peronnel exposé lors de l'utilisation de l'agent de stérilisation de dispositifs médicaux jetables. Les seuls résultats significatifs ont été obtenus par analyse chromosomique de lymphocytes de culture prélevés chez les travailleurs. Des différences significatives pouvaient être observées dans le nombre et les types d'aberrations chromosomiques entre les travailleurs exposés et les témoins non exposés. Les formes chromosomiques quadriradiales et triradiales que l'on retrouve rarement dans les populations non exposées étaient accrues chez les travailleurs exposés. Les lymphocytes de culture présentaient un nombre accru d'échanges de chromatide-soeur chez certaines, mais non chez toutes les personnes exposées. Lorsque le nombre et les types de troubles chromosomiques remarquées parmi le groupe exposé étaient comparés aux valeurs obtenues à partir d'autres mesures, aucune corrélation significative n'était relevée entre les appariements suivants: valeurs obtenues au tableau de la chimie sanguine, nombre et type de lymphocytes, âge de l'employé, antécédents de fumage, taux de fumeurs, années d'exposition et de numération spermatique. Cette expérience porte à recommander la poursuite du contrôle médical des personnes travaillant avec l'oxyde d'éthylène.

Introduction

Ethylene oxide (ETO) is a highly reactive, penetrating alkylating agent with the formula:



It is a known mutagen for a number of test systems, possessing an active group known to react with DNA (1). Its primary use is as an intermediate in the production of chemicals. These include ethylene glycol, polyester fibers, non-ionic surface active agents, glycol ethers, among others. Used as a sterilant of medical equipment and supplies, it also finds application as a fumigant for food, clothing, bedding and pharmaceutical equipment. It has been used widely for over 20 years.

Information obtained from a number of sources including investigations by NIOSH (1), prompted the American Hospital Supply Corporation, which uses ETO for sterilization of disposable medical devices, to undertake an investigation of possible health effects of the gas on its employees.

A pilot study reported by Abrahams (2) in which chromosomal analysis was done on American Hospital Supply Corporation employees exposed to ETO presented evidence of an increased number of chromosome aberrations. These included an overall increase in the total number of aberrations and sister chromatid exchanges, and an increased number of quadriradial and triradial exchanges. The present investigation is a continuation of this pilot study.

Methods

Selection of employees for participation in the study:

Examinations were offered to employees who currently had exposure to ETO. The decision as to whether exposure could have occurred to the employee was made by the supervisor who was familiar with the work assignments and areas in which exposure might occur at each location.

A control group for cytogenetic evaluation was formed from employees at one facility who had not had prior exposure to ETO (Control Group I); they were matched for years of work at the facility and age. In addition, in the cytogenetic studies, each new employee to be assigned to work in the sterilization area served as his own control in that a blood sample was obtained for chromosomal analysis prior to his first exposure (Control Group II).

Plant sites

The study being reported here was conducted at nine plant sites from 1979 through 1980. These facilities were located in the continental United States (facility numbers 1,2,3,4,9) and in Puerto Rico (facility numbers 5,6,7,8). Two concentrations of ETO were used during the sterilization process: Either 100% of 12% and 88% FREON #12. Certain facilities use both.

Exposures

American Hospital Supply Corporation initiated its comprehensive ETO air monitoring program in 1977. Test results from monitoring personnel for the test period 1977 through 1980 indicate 1-40 ppm per 8 hour Time Weighted Average (TWA). Short term excursion levels at the facilities were usually below 75 ppm.

Medical evaluations

Each participant in the study received a complete physical examination evaluating the major body systems and a historical evaluation of previous employment, family diseases, reproductive history, including sexual activity, and past medical events. Laboratory examinations included the following: a complete blood count, urinalysis, chest x-ray, audiometry, visual acuity measurements, pulmonary functions (including vital capacity and FEV_1), sperm counts and SMAC-20, or SMA-12. The examination was carried out according to a common protocol by the attending physician at each plant location.

Cytogenetic evaluations

Cytogenetic studies were conducted on blood from control and exposed groups. One hundred cells were analyzed by karyotyping and twenty cells were analyzed for sister chromatid exchanges (SCEs). These data were expressed in the karyotyping as a percentage of abnormal cells according to the Denver classification as follows:

a. Breaks

b. Exchanges

c. Other unstable forms (Cu)

d. Total unstable forms (Cu)

e. Stable forms (Cs)

f. Total abnormal cells per 100 metaphase plates.

g. Total number of abnormalities per 100 metaphase plates.

Aberrations designated as Cu include rings, dicentrics, fragmentations, double minutes, tricentrics, polycentrics, exchanges (including quadriradials, triradials and regular exchanges). Cs aberrations include translocations, inversions, hyperploidy, or polyploidy, endoreduplications, isochromosomes and accessory chromosomes. Gaps have not been taken into consideration.

SCEs were defined by the number of exchanges per cells averaged over 20 cells. Culturing of cells used in karyotyping was 68 hours, and for the sister chromatid exchanges, 72 hours.

Statistical comparisons

Methods used included the Mann-Witney test, Duncan's multiple range test, standard two-way analysis of variance, Kendall Taub correlation coefficients and an independent group T-test with a computer program for statistical analysis systems, version 79.2.

To control bias in the cytogenic studies, all samples were coded and read blind. Since there were no base-lines on the persons in the original exposed group, it was necessary to obtain a control group of unexposed employees. The original control group consisted of volunteers from one of the larger facilities, who had no known prior exposure to ETO. It was augmented later by persons from all locations on whom examinations were done prior to their employment. Where possible, controls were tested the same day as exposed employees (combined controls-N=141).

Results

Medical evaluations

The combined control group was gathered from 1978 to mid-1981 and we believe it is fairly representative of the normal, unexposed working population. The group's composition was constant throughout. In the combined control group, only the new hires received physical examinations and laboratory tests. All employee groups were evaluated by cytogenetic tests. SCEs were not done on the Group 1 controls. SCEs on the exposed employees in the pilot study were done at 68 hour culture and could not be compared to all the values obtained by culture at 72 hours.

Several new hires in the control group became sterilizer operators and are also included in the 1980 exposed group.

Thirteen employees showing abnormally high numbers of chromosomal aberrations, including quadriradials and elevated SCEs were removed from exposure as a precautionary measure. They are included in both the 1979 and 1980 studies.

There were 79 exposed and 84 unexposed employees given physical examinations and laboratory tests. There were no significant differences in any of the comparisons between the unexposed and exposed groups. Symptoms elicited were mild and not specific; this was in contrast to the study by Garry et al. (3). There were no cases of leukemia or cancer of any kind discovered in the exposed population, or in the unexposed group. There was one death in the exposed group during the study, which was reported as "heart attack".

Cytogenetic studies

A comparison of type and mean numbers of chromosomal aberrations and total aberrant cells of the two control groups, described in the methods section, showed no significant statistical differences (p 0.3), therefore, they were combined in a single control group numbering 141 subjects.

A number of comparisons were then made between the results of the cytogenetic analysis of cells obtained from exposed workers with the controls. Tables 1 and 2 show these data from facilities 1,5 & 9, using primarily 100% ETO, in 1979 and 1980. Table 3 shows results of the comparison of combined controls vs. exposed workers at facility 1 only. The increased number of exchanges, including the distinctive quadriradial, (Figure 2), (4) at facility 1, was the most unusual finding. Results of comparison of combined controls vs. workers at facilities 5 and 9 alone show no significant statistical difference except for Cu (p=0.0075). Comparisons were made of type and mean numbers of chromosomal aberrations and total aberrant cells and SCE in combined controls vs. exposed workers in facilities 2,3,4,6,7, and 8 using 12/88 ETO for both years. There were no significant statistical differences except for Cu (p=0.015) (1979) and SCE (p=0.001) (1980).

Other chromosomal aberrations seen include increases in the number of breaks, Cu cells, and total number of aberrations and total aberrant cells. SCEs were increased over the controls in the cultured lymphocytes of some, but not all, exposed persons (Figure 4).

Table 4 presents a comparison of the cytogenetic results obtained in 1979 and 1980 from exposed workers. There were no significant differences in these results, except SCE increased in 1980 (p=0.026). This suggests that the cytogenetic changes may persist. This may be due to long-lived lymphocytes which may remain in the peripheral blood for a number of years. Several exposed employees were dropped from the exposed groups due to termination and this explains the difference in the population size between 1979 and 1980.

A study was made of the number and types of chromosomal abnormalities found among the exposed group with the values obtained from other measurements made during the study. No significant correlations were found at most locations between the following matches:

1. The value obtained in the blood chemistry profile.

2. The number and type of white cells.

3. Age of the employee.

4 Smoking history.

5. Years of exposure.

6. Sperm counts.

In correlation studies in facilities 1, 5 and 9, only among exposed employees in facility 1 in the 1980 data analysis was there a correlation of laboratory values with cytogenetic findings. At that time, for facility 1, there were noted the following statistically significant correlations:

Alkaline phosphatase to total Cs's (r=0.48)

SGOT to total Cs's (r=0.47)

SGPT to SCE (r=-0.54) and

LDH to total abnormal cells (r=0.37)

There were no significant correlations of blood chemistry and smoking with cytogenetic findings in the facility numbers 2,3,4,6,7 and 8 either in 1979, or 1980.

TABLE 1: Comparison of Type and Mean Numbers of Chromosomal Aberrations and Total Aberrant Cells in Combined Controls vs. Facilities 1, 5, & 9 Exposed Groups Using 100% ETO (1979)

Variable	Controls (N=141)		Exposed (N=28)		P value	Mann-Whitney Test
	mean	s.d.*	mean	s.d.*		
Breaks	2.69	2.04	4.57	2.69	0.0013	0.0003
Exchanges	0.11	0.33	2.75	3.92	0.0014	0.0000
Other CU	1.11	2.22	2.39	2.64	0.0074	0.0004
Total CU	1.21	2.23	5.11	5.95	0.0019	0.0000
Cs	0.62	0.95	0.79	1.40	0.5451	0.7256
Total Aberrations	4.52	3.50	10.64	8.04	0.0005	0.0000
Total Aberrant Cells	4.03	2.47	9.64	6.57	0.0001	0.0000
SCE	9.36 (N=103)	2.13	16.96 (N=15)	8.27	0.0032	0.0000

* Standard deviation

TABLE 2: Comparison of Type and Mean Numbers of Chromosomal Aberrations and Total Aberrant Cells in Combined Controls vs. Facilities 1, 5, & 9 Exposed Groups Using 100% ETO (1980)

Variable	Controls (N=141) mean	Controls (N=141) s.d.*	Exposed (N=30) mean	Exposed (N=30) s.d.*	P value	Mann-Whitney Test
Breaks	2.69	2.04	4.97	2.68	0.0001	0.0000
Exchanges	0.11	0.33	2.53	3.29	0.0004	0.0000
Other CU	1.11	2.22	3.07	2.24	0.0001	0.0000
Total CU	1.21	2.23	5.60	4.15	0.0001	0.0000
Cs	0.62	0.95	1.37	1.70	0.0249	0.0135
Total Aberrations	4.52	3.50	11.63	5.79	0.0001	0.0000
Total Aberrant Cells	4.03	2.47	10.00	5.19	0.0001	0.0000
SCE	9.36 (N=103)	2.13	15.87	6.34	0.0001	0.0000

* Standard deviation

TABLE 3: Comparison of Type and Mean Numbers of Chromosomal Aberrations and Total Aberrant Cells in Combined Controls vs. Exposed Workers of Facility #1 (1979)

Variable	Controls (N=141)		Exposed (N=21)		P value	Mann-Whitney Test
	mean	s.d.*	mean	s.d.*		
Breaks	2.69	2.04	4.52	2.48	0.0003	0.0008
Exchanges	0.11	0.33	3.19	4.29	0.0036	0.0000
Other CU	1.11	2.22	2.52	2.93	0.0098	0.0015
Total CU	1.21	2.23	5.67	6.67	0.0064	0.0000
Cs	0.62	0.95	0.90	1.48	0.3962	0.8791
Total Aberrations	4.52	3.50	11.19	8.44	0.0018	0.0000
Total Aberrant Cells	4.03	2.47	9.95	6.64	0.0006	0.0000
SCE	9.36 (N=103)	2.13	16.96 (N=15)	8.27	0.0032	0.0001

* Standard deviation

TABLE 4: Comparison of Type and Mean Numbers of Chromosomal Aberrations and Total Aberrant Cells in Exposed Groups 1979 vs. 1980

Variable	1979 (N=77) mean	1979 (N=77) s.d.*	1980 (N=61) mean	1980 (N=61) s.d.*	P value	Mann-Whitney Test
Breaks	4.14	3.49	4.31	3.22	0.7712	0.5627
Exchanges	1.27	2.69	1.39	2.58	0.7903	0.5788
Other CU	2.22	3.14	2.13	1.97	0.8381	0.3294
Total CU	3.48	4.79	3.51	3.66	0.9694	0.3137
Cs	0.70	1.10	1.00	1.41	0.1779	0.2169
Total Aberrations	8.39	7.59	8.54	5.76	0.8943	0.3412
Total Aberrant Cells	7.44	6.32	7.57	4.97	0.8937	0.4240
SCE	11.99	6.97	13.50	5.55	0.2407	0.0261

* Standard deviation

There was slight correlation of the number of years of exposure with cytogenetic findings when data from facility numbers 1,5 and 9 were combined. This was true for both 1979 and 1980 (Kendall Taub correlation coefficients).

1979:NC_ur=0.48; exchanges r=0.40; NSCEr=0.41; total aberrations r=0.36; N cells r=0.36.

1980:NC_ur=0.34; exchanges r=0.45; total aberrations r=0.42; N cells r=0.46.

There were no correlations between years of exposure to ETO and cytogenetic findings for the facilities using 12/88 formulation for either of the years studied.

There were no significant correlations (Kendall Taub) of blood chemistry, numbers and types of white cells, or smoking to cytogenetic findings in the controls.

The effect of smoking on SCE values was obtained from analysis of the controls.

	N	Mean SCE	Standard Deviation
Smokers	15	8.9	3.22
Non Smokers	26	8.5	1.56

This small increase (which may be somewhat larger in a greater population) would be lost in the exposed population where the SCE reached as high as 35.7.

It is of interest that of the 13 individuals removed from exposure during the pilot study, 8 were non-smokers, 4 smoked less than 1 pack per day and only one smoked more than 2 packs per day.

Discussion

Shaw (5) in 1970 published an article on human chromosome damage by chemical agents.

Thiess et al. (6) reported on a study of chromosome changes in lymphocyte cultures from workers exposed to alkylene oxides and other compounds. This author classified the employees into four groups according to their exposure history: Exposure for more than 20 years, exposure for less than 20 years, long term exposure together with documented inhalation or skin contact and significant accidental exposure. Only the group having exposure for more than 20 years had a significant increase in aberration rate. On reviewing these data, it is not clear whether the differences may be due to age alone. Only % aberrant cells were reported - neither specific aberrations nor sister-chromatid exchanges were noted.

There have been a number of reports of the monitoring possibilities of the SCEs in cultured human lymphocytes; (7,8) and on the effects of chemicals on the SCE (9). In the present study, the mean SCE in the controls was 9.44 in the controls with a range of 3.9 to 16.2. In the 1979 data analysis of the exposed group at facilities 1,5 and 9, the mean was 17.0 with a minimum of 7 and a maximum of 35.7. In the same group in the 1980 data analysis, the mean was 15.9 with a minimum of 5.8 and a maximum of 35.7.

In 1979, in the combined facilities using the 12/88 mixture, the SCE mean was 8.7 with a range of 4.4 to 16.20. In the same group in 1980, the mean of the SCEs was 11.1 with a range of 5.8 to 17.1. Based on our review and recent monitoring data, the SCE appears to be a very sensitive indicator of recent exposure. It appears to show an increase prior to the appearance of chromosome aberrations and a decrease when exposure ceases prior to the decrease in chromosome aberration.

It should be borne in mind that the individuals included in the exposed groups were exposed to varying amounts of ETO, thereby diluting the results.

While the above findings can in no way be predictive of future illness (10) it was believed prudent and feasible to remove from exposure certain employees showing quadriradial and triradial chromosome forms and elevated SCEs and to reduce exposure to ETO.

Based on these studies, we believe that a medical program should be instituted for the assessment of the health of all persons working with ETO. When possible, examinations should be done prior to assignment to work with this substance. Periodic cytogenetic re-evaluations should be performed not less than once a year so long as individuals work in exposure areas. Evaluations at the time of termination are in order.

Monitoring of the American Hospital Supply Corporation's exposed employees is being continued. Protection of exposed employees should include the following procedures.

1. Careful monitoring of any area in which ETO is used, with proper ventilation control to reduce the airborne concentration.

2. Medical evaluation, including elicitation of a careful family history, reproductive history and past medical events, laboratory assessment of the possible documentable effects on health, including possible effects on the blood,

liver and reproductive organs, respiratory tract and basic cellular structures.

3. A cytogenetic screening program should be conducted on a periodic basis (11).

4. Guidelines should be prepared for supervisors and panel physicians regarding the nature and extent of counselling to be given employees about the possible risks associated with working with ETO.

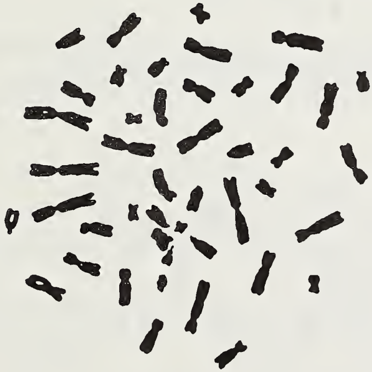


Figure 1: Normal Lymphocyte Metaphase Plate (Non-Exposed)

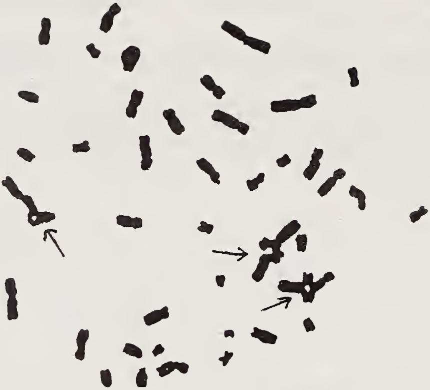


Figure 2: Lymphocyte Metaphase Plate from Exposed Worker Showing Quadriradial and Triradial Aberrations

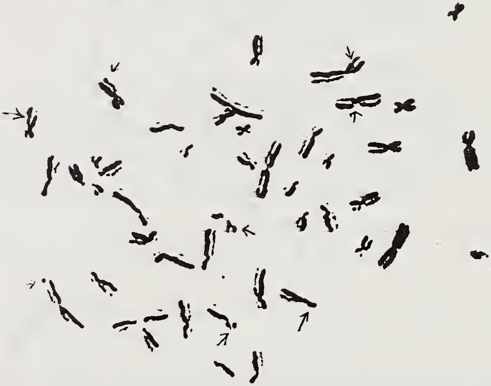


Figure 3: Normal Lymphocyte Metaphase Plate Showing Few Sister Chromatic Exchanges (Non-Exposed)

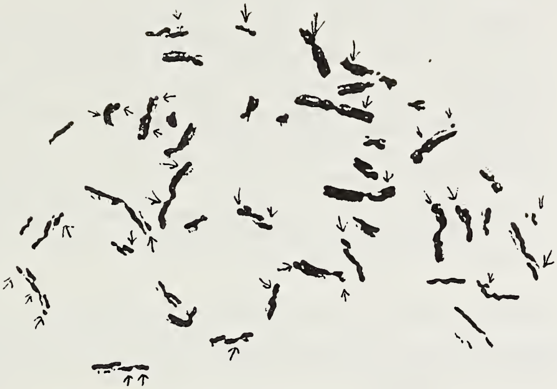


Figure 4: Lymphocyte Metaphase Plate from Eto-Exposed Worker Showing Many Sister-Chromatid Exchanges

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REACTIONS DERMATOLOGIQUES DANS L'INDUSTRIE DES FIBRES SYNTHETIQUES

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Abstract

Two defined groups of fibres are made today in industry:

1. Fibres like rayon and acetate are obtained after chemical treatment of natural fibres (e.g. cellulose).

2. Synthetic fibres like nylon and polyesters are obtained by different chemical or physical processes, where synthetic products are used.

Our study concerned nylon 6/6, a polyamide obtained after the condensation of hexamethylenediamine with the aid of adipic acids. The process is described. It is probable that small quantities of hexamethylenediamine are released and combined (phase stretch) with the coal based anti-static solution and remain in the finished product.

The hexamethylenediamine is a highly alkaline product, causing serious burns to the skin and, sometimes, a severe sensitivity and inflammation, a true contact dermatitis.

Four female factory workers are presented with different types of skin conditions acquired during their work. One of them was hospitalized with a severe case of bullous eruptions on the legs. After prolonged treatment, she was left with hyperpigmentation scarring. The epidemiologic investigation led us to three other cases with dermatitis related to synthetic fibres.

Clinical and laboratory tests, including the patch test, enabled us to conclude that hexamethylenediamine, even in very minute quantities, was the factor in producing the dermatological reactions, not only skin burns, but also an over or acute sensitivity.

*presented paper at Conference

Un jour du mois d'Octobre 1982, une jeune ouvrière d'une usine où l'on utilise des fibres synthétiques a été hospitalisée à la suite d'une apparition relativement unique d'une éruption bouleuse localisée sur les jambes. A la suite d'examens, nous sommes arrivés à la conclusion qu'un facteur chimique pouvait en être la cause.

L'enquête épidémiologique dans l'usine, effectuée par le département de médicine du travail de la région de Haifa et de Galilée, nous a conduit à la découverte de trois autres ouvrières de la même usine, qui ont présenté des réactions dermatologiques liées aux conditions de travail. C'est ainsi que nous nous sommes concentrés sur la Hexamethylendiamine, un des principaux constituants du Nylon 6/6, comme agent causal des phénomènes toxiques et, allergiques, apparus en même temps.

La jeune fille K.H., 20 ans, née en Israël, a été hospitalisée, comme nous l'avons déjà affirmé au mois d'Octobre, 1982, pour une éruption bouleuse aigüe sur les jambes, accompagnée de brûlures et d'une réaction prurigineuse intense, qui s'est dévelopée au cours d'une semaine. On n'a pas noté de troubles systémiques, tel état fébril, malaises, ou éruptions plus étendues qu'au jour de l'hospitalisation. Nous nous sommes trouvés devant un "status quo" comme au premier jour.

Les examens physiques généraux ont été normaux sauf pour l'aspect de la peau. L'éruption s'est présentée sous forme des vésicules buleuses, rondes, ayant une diamètre d'un demi à 3 centimètres, bien tendues, et contenant un liquide visqueux clair. Les vésicules étaient presque toutes isolées une de l'autre, très peu liées, et se sont trouvées sur un fond de peau saine. La localisation était surtout sur la partie antérieure et postérieure des jambes et s'éteudait étendue jusqu'aux fesses. Nous n'avons pas décelé d'autres localisations.

Les examens de laboratoire, l'hémo et léucogramme, la vitesse de sédimentation, le glucose, la phosphatase, alcaline, les électrolites, étaient faces normaux. Le test Nikolski sur la peau a été négatif, cependant l'examen citologique du liquide vésiculaire a révélé des cellules inflammatoires sans formations épidermiques (test Tzang - négatif).

Dans cette phase n'ayant aucun agent causal bien défini, nous nous sommes limité à un traitement local, tel drainage aseptique et compresses. L'amélioration a été visible et à la fin, des cicatrices délicates, hyperpigmentées sur toute la surface des vésicules disparues sont réstées (1-4).

Le manque d'une réaction systémique, les résultats de laboratoire normaux et le manque de signes cliniques indiquaient que ces phénomènes vésiculaires ressemblaient au pemphigus ou à une autre maladie allergique généralisée, nous a dirigé vers la possibilité d'une exposition à un agent toxique accidental possible.

L'anamnèse nous a permis, dans quelque mesure, d'entrevoir une réaction probable aux fibres synthétiques. C'est ainsi que nous avons commencé notre enquête épidémiologique, qui a été cette fois bien justifiée. Nous nous sommes concentrés surtout sur l'apparence d'autres cas, qui ont souffert des affections allérgiques ou dèrmatologiques, à la suite du travail avec des fibres synthétiques. La mission n'a pas été facile, à cause des jeunes filles qui ont eu des réserves à nous faire connaître et voir ces aspects. Nous nous sommes entretenues avec les directeurs des usines, avec les représentants des ouvrières et avec les médecins, qui suirvellent ces usines. En fin de compte, nous avons découvert trois autres jeunes ouvrières de la même usine, qui ont subi dans le passé des traitements - dit on allérgiques - ou des affections dermatologiques, qu'on pourra lier avec les conditions de travail - à une certaine exposition à un agent chimique. Deux des ouvrières (les malades 2 et 4) ont même passé des tests à leur polycliniques et chez l'une (4) on a trouvé une sensibilité aux poussières.

Nous avons effectué de nouveau une anamnèse détaillée, des examens physiques et des examens de laboratoire de routine, (y compris K.H., le cas hospitalisé). En plus, nous avons effectué le "Patch Test" avec tous les produits compris dans le processus de fabrication à l'usine mère (A) et à l'usine où nous avons découvert les quatres cas citées (B).

Le "Patch Test" a été effectué d'après la méthode standard (1,2) et été interprété après 48 et 96 h. de la manière suivante (-), sans réaction, (+) réaction erithémateuse faible, (++) réaction erithémateuse édémateuse forte.

Les produits examinés ont été le Nylon 6/6 comme matière première (dans l'usine mère), le Nylon 6/6 (après avoir passé certaines phases) produit final (sans coloration), le Lysolfix V4, (solution) houilleuse antistatique, utilisé dans la phase stretch et l'ultran, détergent (produit Ciba-Geigy).

Les examens nous ont montré les faits suivants:

Le Tableau 1 présente des détails sur les ouvrières. Comme vous le voyez, toutes les quatres sont jeunes (âgé de 18 à 22 ans), toutes les quatres n'ont pas été malades et n'ont pas souffert d'aucune affection dermatologique dans le passé (pas elles-mêmes et pas dans leurs familles). Nous pouvons encore ajouter que toutes les quatres sont de la même région et des villages assez rapprochés les uns des autres.

TABLEAU 1: Données Epidémiologiques de 4 Ouvrières d'une Usine de Fibres Synthétiques

CAS NO.	NOM	SEXE	AGE (ANNEES)	ANCIENNETE DANS L'USINE (MOIS)	ATOPIE	
					PERSONNELLE	FAMILIALE
1.	K.H.	F	20	24	-	-
2.	C.B.	F	19	9	-	-
3.	Z.A.	F	18	28	-	-
4.	B.A.	F	22	60	+	-

Le Tableau 2 présente des détails cliniques dermatologiques que nous avons trouvé et des détails au sujet de leur ancienneté dans l'usine, au moment où les manifestations cliniques ont commencé.

TABLEAU 2: Aspects Cliniques

CAS NO.	NOM	1ere APPARUTION APRES LE DEBUT DU TRAVAIL (MOIS)	ASPECTS CLINIQUES
1.	K.H.	6	Deux épisodes d'une éruption bouleuse aîgue, localisée sur les deux cuisses, Sept. 28, Aout 83.
2.	C.B.*	1	Récidive d'éruptions avec marques érythémateuses et démangeaisons. Au début localisées sur les mains et jambes, puis étendues sur le tronc et le visage.
3.	Z.A.	19	Un seul épisode d'une éruption avec démangeaisons sur l'abdomen; a duré 3 semaines en laissant des surfaces dépigmentées.
4.	B.A.	1	Récidive d'épisodes de prurite accompagnée de rhinite allergique.

*A dû quitter son travail après 8 mois de maladie.
Un mois plus tard - aucun symptômes.

Chez 2 ouvrières les phénomènes cliniques sont apparus dans le courant d'un mois seulement après le commencement du travail, cependant que chez les deux autres, les manifestations sont apparues lentement sur une période plusieurs mois.

Chez la malade 2 les phénomènes ont été violents et elle a dû quitter le travail (usine B) après 8 mois. Un mois plus tard elle n'a plus présenté de symptôme clinique. La malade 4 a présenté des manifestations d'atopie basale ayant des fluctuations d'aggravation et relâchement, en fonction de l'exposition au tissu des fibres synthétiques.

Les malades 1 et 3 ont présenté des fortes manifestations, une seule fois; la première 1 mois et la deuxième 3 mois après le commencement du travail.

Le Tableau 3 présente les résultats du "Patch Test". Trois des 4 ouvrières ont présenté des réactions relativement fortes (1). Toutes les 3 ont réagi au produit final (tissu) et presque pas du tout à la matière première (les fibres initiales). Deux d'entre elles ont réagi au Lissilfix (l'ouvrière atopique n'a pas réagi). On n'a pas enregistré de réactions à l'Ultran.

TABLEAU 3: Résultats du "Patch test" Effectué sur les Ouvrières d'une Usine de Fibres Synthétiques (Fév. Juin 83)

Matière	K.H.		C.B.		Z.A.		B.A.	
	Fév.	Juin	Fév.	Juin	Fév.	Juin	Fév.	Juin
Nylon 6/6 (matière première)	-	-	-	-	-	-	-	-
Nylon (tissu)	+	-	-	+	+	-	-	-
Ultran	-	-	-	-	-	-	-	-
Lissolfix	-	+	+	-	-	-	-	-

- pas de réaction
+ réaction positive (allergie)

Deux groupes délimités de fibres sont produits aujourd'hui dans l'industrie.

1. Les fibres naturelles (par exemple la cellulose), desquelles on peut obtenir par example le Rayon, le Rayon Acetate, etc. Dans le procéssus de fabrication de ces fibres, on utilise des produits comme le formaldehyde, le bicromate de potassium, ainsi que des colorants différents, comme par example l'antraquinon, etc. Tous ces produits sont connus comme étant très allergisants. Ils pourraient aussi fournir parfois une indication sur la "clothing dermatitis".

2. Les fibres synthétiques comme par exemple les Polyesters, dérivatifs du Polyvinyl, comme Polyacrylonitrile, PVC, le Nylon 6/6, le Nylon 6/10, le Nylon 11, le Nomex, etc. C'est vers 1935 que commence l'ère relativement nouvelle de Wallace Carothers et de DuPont de Nemours de la production des fibres synthétiques. Ces fibres sont obtenus de produits synthétiques par des procédés physiques, chimiques ou physico-chimiques, et sont d'après Cywie et al (9) dans quelque mesure moins agréssifs du point de vue dermatologique que ceux du premier groupe. Dans notre étude nous nous limitons seulement au Nylon 6/6, polyamide, produit grâce a un processus de condensation du Hexamethylendiamine et de l'acide adypic en proportion 6 sur 6.

Le produit chaud passe par un "extruder" et se solidifie après avoir reçu un courant d'air frais. Dans cette phase une certaine quantité de Hexamethylendiamine est libérée. La possibilité qu'une certaine quantité de Hexamethylendiamine entre en combination avec le Lyssolfix V4 (solution houilleuse antistatique) est bien possible. Ce produit peut rester lié avec le Lyssolfix même après l'usage du détergent Ultran jusqu'à la phase finale du tissue - de couleur blanche.

Du point de vue de la médicine du travail, il semble (et c'est bien concevable) que la Hexamethylendiamine reste l'agent actif de fabrication. Nous n'avons rien trouvé dans la littérature sur une action toxique ou allergissante de l'acide adypique.

D'autre part, le Hexamethylendiamine est connu comme un produit alcalinisant fort, qui est capable de produite des brûlures fortes de la peau. En plus, le produit peut provoquer une forte sensibilité: une véritable dermatite de contact allergique.

Les manifestations cliniques décrites ont été en partie toxiques et d'autre part allérgiques. La malade No. 1 K.H., qui a présenté une éruption bouleuse éritémateuse a laissé une hyperpigmentation, c'est-à-dire un état irritatif, semblable à une brûlure. Cette ouvrière et les autres deux, ont présenté au "Patch Test" des réactions allergiques.

Etant donné, et c'est bien concevable, que les quantités de Hexamethylendiamine ont été infinitéssimales, la réaction au Patch Test a été seulement allérgissante.

La localisation des manifestations dermatologiques a été surtout sur les jambes, à la partie antérieure et postérieure, l'abdomen et les mains. Il faut remarquer, que pendant le contrôle du tissu en extension, une bonne partie se prolonge et glisse sur le ventre, jambes et chaires, et c'est ainsi que nous pensons expliquer les localisations.

Il faut aussi souligner la période chaude, septembre-octobre (en Israël, c'est la période des khamsins, vent sec), que ces phénomènes se sont produits. D'après certains auteurs, c'est une période favorisante pour une actions des agents extérieurs sur la peau, spécialement, et sur tous les organes au pluriel.

Nous pensons, que cette étude préliminaire de la présentation de ces 4 cas d'un nombre total de 60 ouvrières, mérite d'être continuée et, surtout, afin d'établir le rôle du Hexamethylendiamine.

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FORMALDEHYDE SENSITIVITY FOLLOWING EXPOSURE TO BUILDING MATERIALS

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Abstract

Eight patients who were exposed to the inside of mobile homes, new plywood, particle board or wall board developed formaldehyde sensitivity. These patients often were found to have T lymphocytes below 1000 cu mm range (control is 1400-1800). They were also found to be sensitive to inhaled challenges of formaldehyde at the level of 0.5 ppm. In addition it was noted that these patients developed symptoms upon exposure to minute doses of other inhaled chemicals. Double blind challenges of low levels confirmed the development of widespread chemical sensitivity. The doses used were phenol (<0.02ppm), chlorine (<0.33 ppm), pesticide (2,4 DNP)(<0.00134 ppm), formaldehyde (<0.2 ppm), and petroleum alcohol (<0.5 ppm). Intradermal injections of formaldehyde showed a high degree of correlation of skin sensitive reactions and inhaled challenges.

Résumé

Huit sujets qui avaient été exposés à l'environnement intérieur de maisons mobiles, au nouveau contreplaqué, aux feuilles de particules de bois pressé ou planche murale ont acquis une sensibilité à la formaldéhyde. Ces patients ont souvent présenté une concentration de lymphocytes T inférieure au niveau 1000 cu mm (le témoin est 1400-1800). Ils étaient également sensibles à l'épreuve d'inhalation de formaldéhyde au taux de 0.5 ppm. De plus, il a été noté que ces patients avaient développé des symptômes après exposition à des minimes quantités d'autres vapeurs chimiques. Des épreuves à double tèmoin avec de faibles concentrations ont confirmé l'apparition d'une sensibilité chimique généralisée. Les doses utilisées ont inclus du phénol (<0.02 ppm), du chlore (<0.33 ppm), un pesticide (2,4DNP)(<0.00134 ppm), de la formaldéhyde (<0.2 ppm), et de l'alcool de pétrole (<0.5 ppm). Des injections intradermiques de formaldéhyde ont montré un degré élevé de corrélation entre les réactions de sensibilité cutanée et les épreuves d'inhalation.

LIMITES D'EVALUATION DES RISQUES DE LA POLLUTION DE L'AIR: CONCENTRATIONS PHYSIOLOGIQUES EN POLLUANTS GAZEUX DANS L'AIR EXPIRE?

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Abstract

It is very difficult to evaluate the risks due to pollution when exposure is low. Urban atmospheres always contain a certain number of pollutants which can be easily identified by modern methods. To a certain degree, the study of expired air allows the specification of human contamination when an individual has been exposed to an industrial atmosphere or when he has consumed products liable to break down releasing volatile substances. In addition, some gaseous elements found in expired air result from biologic reaction dependent or not on the alimentary state. The analytical study on the ppb scale (10^{-9} vol.) is only one of the ways to define the resultant of the different phenomena at a given time; a very complex situation in spite of the precision and reliability of measures obtained with mass spectrograph materials. A comparison of clinical studies, pharmacologic and toxicokinetic data and quantitative analyses allows the proposal of conclusions which conform to current knowledge and the preparation of acceptable epidemiologic studies.

Résumé

L'évaluation des risques dûs à la pollution de l'air est très difficile lorsque l'exposition est faible. Les atmosphères urbaines comprennent en permanence un certain nombre de polluants facilement identifiés par les méthodes modernes. L'étude de l'air expiré permet dans une certaine mesure de préciser les contaminations humaines lorsqu'un sujet a été exposé à une atmosphère industrielle ou lorsqu'il a consommé des produits susceptibles de se dégrader en libérant des substances volatiles. En outre, certains éléments gazeux retrouvés dans l'air expiré proviennent de réactions biologiques dépendant ou non de l'état alimentaire. L'étude analytique à l'échelle du ppb (10^{-9} vol.) n'est qu'un des moyens de définir la résultante des différents phénomènes à un moment donné, situation très complexe malgré la précision et la sécurité des mesures obtenues avec des matériaux du type spectrographe de

masse. Une confrontation des études cliniques, des données pharmaco et toxicocinétiques et des dosages ponctuels permet de proposer des conclusions conformes aux connaissances actuelles et de préparer des études épidémiologiques acceptables.

Matériel et méthodes

Pour des raisons évidentes, les techniques non invasives sont toujours préférées et présentent l'avantage de permettre de fréquentes déterminations: les mesures dans l'air expiré constituent de ce point de vue une méthode de choix.

Le résultat recherché était une appréciation des limites accessibles avec des méthodes très sensibles. Par exemple, le taux de benzène dans l'air expiré d'un ouvrier exposé à une atmosphère de l'ordre de 20 ppm est à la fin de la journée de travail, dix minutes après l'arrêt de l'ordre de 2 ppm et tombe le lendemain matin à 0,1 ppm. La quantité de la mesure et sa validation dépend donc du délai de mise en oeuvre de l'exploration et le gain de sensibilité d'un facteur 100 ou 1000 permet de garder une possibilité de détection après un arrêt de travail de plus d'une journée, ce qui s'observe fréquemment dans les consultations de pathologie professionnelle.

On retrouve décrites dans la bibliographie de nombreuses méthodes permettant ces mesures sur l'air expiré. La plupart font appel à la chromatographie en phase gazeuse (CPG) avec absorption préalable sur un gel de silice.

Sherwood et Carter (1970) utilisent une absorption sur gel de silice suivie d'une élution par des vapeurs d'éthanol puis d'une CPG. Cette méthode ne peut plus être considérée comme suffisamment reproductible et sensible pour la détection de taux très faibles.

Gage et coll. (1977) ont décrit une méthode plus sensible que la précédente qui permettrait de détecter le benzène, l'hexane, le n butanol, l'acétone et le trichloréthylène. Ils ont comparé les taux retrouvés dans l'atmosphère et dans l'air expiré.

Nous avons utilisé un spectrographe de masse PETRA, appareil très sensible et bien adapté aux études professionnelles, car facilement mobilisable et d'un emploi simple. Son avantage est que, pour un coût comparable à celui d'une batterie de chromatographes, les résultats peuvent être obtenus sur plusieurs produits isolés successivement ou même avec des mélanges en limitant l'analyse aux constituants principaux sans aucune modification de l'appareil et par interprétation directe. La relative simplicité correspond en fait à un haut degré de technicité pour une mise en oeuvre fiable.

Le spectromètre de masse PETRA permet l'identification de doses très faibles de produits volatils, directement ou par l'intermédiaire des fragments de dégradation moléculaire: les molécules de vapeurs sont soumises à un bombardement d'électrons dans la source d'ions et se transforment ainsi en ions positifs. Ces ions positifs passent ensuite dans un spectro de masse quadrupole où ils sont séparés selon leur poids moléculaire.

Très souvent, l'ion moléculaire n'est pas le pic le plus important et même parfois il peut être totalement absent du spectre.

L'originalité de l'appareil réside, outre sa simplicité d'utilisation, dans la possibilité de séquestration de l'échantillon à analyser dans une "boucle de mesure" permettant ainsi de faire plusieurs mesures sur la même expiration, le couplage à un enregistreur permet de garder une trace de l'examen, donc éventuellement une comparaison avec un examen ultérieur. (schéma de l'appareil).

Système d'Introduction

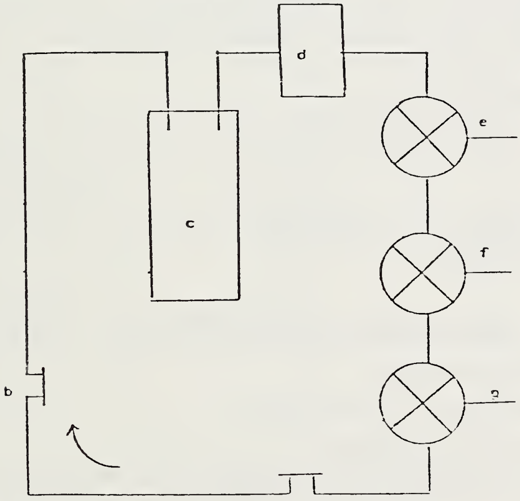


Schéma de l'Appareil

Légende

Système d'introduction

a) Membrane d'introduction
b) Septum
c) Réservoir d'un litre
d) Pompe d'un débit de 5 litres/minute
e) Sortie
f) Entrée du gaz destiné au rinçage de la boucle
g) Entrée de l'échantillon à analyser.

Appareil Petra

Flush (f) :

Cette position permet d'introduire de l'air pur dans la boucle qui reste ouverte et d'enlever toute trace de l'échantillo précédent en quelques minutes.

Calibration :

La boucle est fermée et le gaz circule à travers le système, le réservoir contient un litre d'air (ou du gaz ayant servi au rinçage de la boucle). On peut donc injecter à l'aide d'une seringue à gaz une quantité infime de produit.

Sample (g) :

Le gaz passe immédiatement à travers la membrane et est rejeté. Ceci permet une analyse rapide ou une analyse en continu.

Vide :

L'appareil est équipé d'un kit de pompage primaire cryostatique. Le haut vide est obtenu par une pompe diode de 60 l/s qui maintient la pression à
1×10^{-6} torr.

I. Détéction dans l'Air Expiré Après Contamination Regulière et Importante (Toxicologie Professionnelle)

Mesures de référence

Chromatographie en phase gazeuse

Spectromètrie infrarouge

L'application de deux méthodes datant maintenant de plus de 20 ans, a pris toute sa valeur lors du développement de la détection des dérivés halogénés et nitrés par le détecteur à capture d'électrons en particulier au cours des travaux de STEWART RD 1963 et 1965.

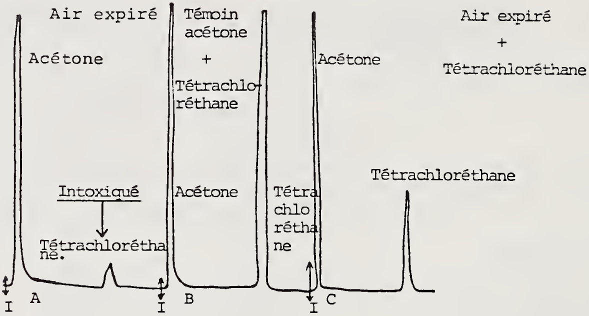
A cette époque, le dépistage a été défini par une sensibilité de l'ordre de 2 ppm en trichloréthylène, 0,5 ppm en tétrachlorure de carbone avec un spectromètre à infrarouge équipé d'une cellule à large bande passante, d'une fraction de ppm en chromatographie en phase gazeuse (CPG) et de quelques ppb pour les solvants halogénés (CPG).

TABLEAU 1: Sensibilité de la Chromatographie en Phase Gazeuse et de la Spectrométrie Infrarouge pour Quelques Gaz et Vapeurs Usuels

Produit	Sensibilité en PPM	
	Chromatographie phase gazeuse	Spectrométrie infrarouge
Acétone	0.1	5
Alcool éthylique	0.1	5
Alcool méthylique	0.2	5
Benzène	0.1	20
Chloroforme	0.01	1
Chloropicrine	0.5	2
Chlorure de méthyle	0.2	30
Chlorure de méthylène	0.1	2
CO_2	100	5
CO	5	20
Cyclohexane	0.1	40
Essence	1	5
Essence de térébenthine	0.4	10
Ether éthylique	0.1	5
Fréon 12	0.5	1
Oxyde d'éthylène	0.1	5
Perchloréthylène	0.01	2
Phosgène		1
Tétrachlorure de carbone	0.001	0.5
Toluène	0.3	5
Trichloréthylène	0.01	2
Xylène	0.1	10

Tétrachloréthane

La figure 1 montre la détection chez un sujet intoxiqué (20 ml d'un liquide inconnu) de tétrachloréthane dans l'air expiré, quinze heures après l'intoxication. Le toxique est encore parfaitement identifiable malgré une respiration assistée avec ventilation forcée (Pebay-Peyroula F., et Nicaise A.M.).



Chromatographie de l'air expiré.

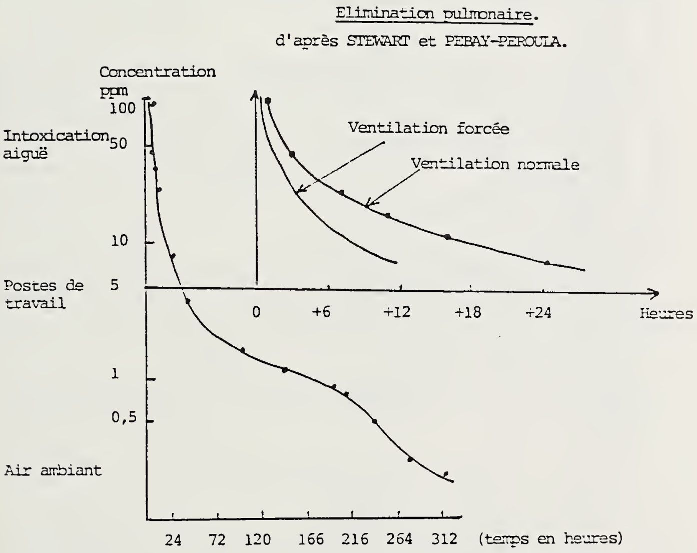
Figure 1: Intoxication par le Tétrachloréthane

A cette époque la cinétique d'élimination dans l'air expiré avait permis la mise au point de l'hyperventilation forcée pour réduire le plus vite possible la présence de toxique à des taux dangereux dans l'organisme de l'intoxiqué.

Tétrachloréthylène

La figure 2 permet de préciser la phase utile de l'intervention thérapeutique pendant les douze premières heures et donne une information supplémentaire sur la phase d'élimination d'un solvant chloré dans l'organisme humain.

La très longue durée de présence du toxique à des taux faibles (10 à 15 jours) est aussi un argument supplémentaire en faveur de la recherche d'une détection systématique des taux les plus faibles par des procédés nouveaux qui doivent être nécessairement capables d'évaluer quelques ppb.

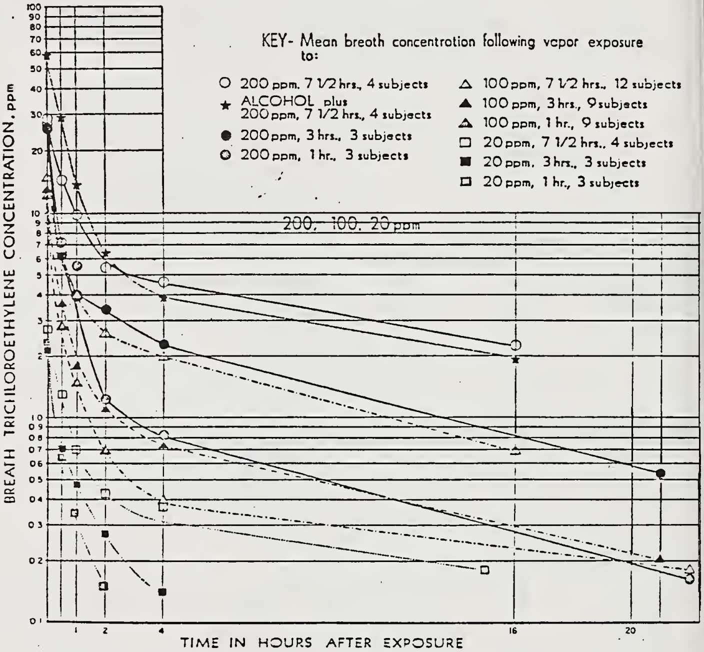


Elimination pulmonaire.
d'après STEWART et PEBAY-PEROULA.

Figure 2: Inhalation Accidentelle de Tétrachloréthylène

Trichloroéthylène

Pour le trichloroéthylène, produit contaminant très banal des atmosphères industrielles et des atmosphères domestiques, une première indication est fournie par les travaux de très nombreux auteurs dont STEWART (1974) montrant la nécessité d'une sensibilité de dépistage largement inférieur à 100 ppb pour l'étude des sujets non professionnellement exposés.



(The TCE postexposure breath decay curves obtained from adults who were exposed for periods of one, three, and 7 1/2 hours trichloroethylene vapor, 20, 100, and 200 ppm)

Figure 3: Trichloroethylene Breath Decay Curves

Détection dans l'air expiré après séjour hors atmosphère contaminée (toxicologie environnmentale)

L'appareillage qui a été implanté à la Clinique Toxicologique a d'abord été orienté vers la consultation de maladies professionnelles.

TABLEAU 2: Limites de Détection (Potentielle. Comparaison avec les possibilités de la CPG

Composé	Amélioration potentielle (p. 2 CPG)	Concentration minimale détectable ppb = 10^{-3} ppm
Acétone	x 10	10
Acylonitrile	x 100	2
Chloro-3 propène-1	x 10	9
Benzène	x 25	4
Benzoquinone		20
Chlorobromo-2 benzène		5
Sulfure de carbone		1
Tétrachlorure de carbone	x 0.1	10
Cyclohexane	x 100	1
Dichloro-1,2 éthane		10
Chlorure de méthylène	x 10	10
Dioxane-1,4	x 100	1
Epichlorhydrine		20
Alcool éthylique	équival	50
Ethyl benzène	x 20	2
Oxyde d'éthylène	équival	50
n-hexane	x 50	2
Alcool isopropylique	x 3	30
Nitrate d'isopropylène glycol		20
Méthylisobutyl cétone	x 25	6
Nitrobenzène	équival	20
Perchloréthylène	équival	5
Oxyde de propylène	x 10	10
Isocyanate de n-propyl		10
Styrène	x 10	10
Anhydride sulfureux		500
Plomb tetraéthyl	équival	30
Plomb tetraméthyl	équival	25
Toluène	x 100	1
Isocyanate de toluène		10
Trichloréthylène	équival	4
Chlorure de vinyle		20
Xylène	x 50	2

Les limites de détection des principaux polluants industriels et domestiques recherchés chez des sujets très différents sont évalués dans le tableau (2).

La sensibilité ne peut être comparée avec celle de la spectrographie infrarouge, trop faible, et montre un gain potentiel important par rapport à plusieurs des limites obtenues en CPG, avec pourtant une nette réserve sur le terme "gain-potentiel". Celui-ci indique une limite technologique mais ne précise pas la zone d'incertitude qui varie selon les ambiances et constitue un bruit de fond parfois élevé en particulier du fait du tabagisme.

La cinétique générale des produits volatiles liposolubles fait en général apparaître trois types d'échanges (ou de compartiments), l'un très cours quelques dizaines de minutes, l'autre long plusieurs heures (tissus), le troisième très long plusieurs jours (tissus adipeux, moëlle osseuse). L'exploration de l'individu après plus de 15 heures de séjour en atmosphère non contaminée permet d'atteindre le troisième type de détection.

Comme les études sur l'air expiré après expositions industrielles sont maintenant nombreuses, nous nous sommes intéressés surtout aux situations d'exposition ponctuelles, très limitées et de travail protégé.

Réactifs de Référence

Leur fabrication est indispensable et délicate; afin d'obtenir des comparaisons rapidement utilisables en pratique, il est indispensable de s'équiper en bouteilles de gaz comprimé comprenant les solvants à mesurer à des dilutions comparables à celles de l'air expiré.

Nous avons participé à la fabrication d'étalons gazeux du benzène (C_6H_6), pour étudier d'abord les corrélations entre hémopathies bénignes et présence de benzène dans l'atmosphère de travail, ce qui a permis:

- d'identifier les produits purs très dilués,
- d'identifier des mélanges relativement simples, dans l'air et dans l'air expiré, sans que l'on puisse parfaitement indentifier chaque élément à la limite inférieure de détection.

La preparation de l'étalon CS_2 n'a pu être stabilisée.

Dans la suite de l'exposé, le terme traces indique que la deéection a été effectée à un taux probable inférieur à trois fois la sensibilité limite pratique sur produit pur. Il n'est pas possible de donner à une telle mesure une valeur quantitative acceptable.

Solvants aromatiques

Les méthodes et résultats obtenus sur solvants et peintures ont été obtenus par l'examen du gaz de distillation spontanée en système clos (head space technique).

Cette méthode très générale est utilisable pour les produits liquides de consommation courante come pour les echantillons biologiques.

	Sensibilite limite pratique en ppb sur produit pur*
Benzene	4
Toluene	1
Dimethylformamide	10
Tetrachlorethylene	4
Cyclohexanone	2
Trichloroethylene	4
Cycloyexanone	2
Carbamate d'ethyle	2
Dichloromethane	10
CS_2	*

*probablement 5

Benzène C_6H_6 :

m/e	78	51	52	50	39	79	76	35	74
%	100	20.5	19.6	17.9	14.1	6.5	6.2	6.1	4.8

Référence toxicologique

Taux dans l'air expiré de l'ordre de 5 à 40 ppb chez des sujets normaux. Présence d'hydro-carbures aromatiques et de benzène dans la fumée de cigarette (de l'ordre de n X 10 ppm).

Un examen pratiqué sur un peintre en carrosserie automobile en fin de journée a révélé des traces de benzène (78-79-50-51-52), des traces d'alcools et d'autres solvants, alors que la détection atmosphérique par tube sensible à 5 ppm avait été négative.

Il n'a pas été possible de trouver des traces de benzène chez une secrétaire qui pourtant emploie des produits contenant du benzène en quantité démontrable. Par exemple, le vernis correcteur dont se sert fréquemment cette personne contient dans son spectre les pics caractéristiques 50-51-52-39-76-78 et 79 du benzène (taux global inférieur à 1%).

Toluène $C_6H_5CH_3$:

m/e	91	92	39	65	51	63	90	50	27
%	100	78.5	20.6	13.8	10.7	10.1	9.1	7.1	6

Un dosage a été effectué sur une laborantine, après un quart d'heure de manipulation de toluène sous hotte. Aucun des pics caractèristiques du toluène n'a pu être relevé. Le spectre ne laissait apparaître que les pics habituels de témoins non fumeurs et sans trace d'alcool.

Une autre laborantine a montré la présence très nette de toluène (de l'ordre de 10 ppb) après une journée de manipulation sous hotte de ce produit.

Un sérigraphiste exposé aux vapeurs de toluène et de cyclohexanone a présenté des traces (de l'ordre de 3 ppb), l'examen ayant été pratiqué un jour de repos.

Une jeune femme employée dans une usine de condensateurs électriques et exposée aux vapeurs de toluène, xylène, trichloroéthylène etc..., n'avait aucune trace de ces produits; l'analyse a été fait après un arrêt de travail prolongé de plus de 15 jours.

Une laborantine de l'Hôpital de Bicêtre manipulant très irrégulière rement du toluène est venue faire effectuer un dosage en début d'après-midi; les pics révélaient un mélange de solvants et d'alcool, non identifiables même qualitativement.

Tétrachloroéthylène

m/e	166	164	129	131	168	47	94	35
%		786	686	655	484	415	398	352

Cas étudié

Nous avons examiné, après une période de travail de deux heures, un jeune employé d'une entreprise de nettoyage de moquettes qui souffrait de malaises graves dès qu'il était en présence de perchloréthylène (tétrachloréthylène). Détection positive (de l'ordre de 1 ppm).

Diméthylformamide

m/e	44	73	42	28	15	30	29	18	43
%		861	466	397	386	309	234	163	107

Cas étudié

Une jeune femme restaurant des tableaux et se servant de diméthylformamide est venue pour contrôler l'efficacité du masque de protection dont elle se sert: effectivement, aucune trace de diméthylformamide n'a pu être relevée.

Sulfure de carbone. Dérivés du disulfirame et traitement des éthyliques chroniques :

Le Disulfirame (Espéral) utilisé dans les cures de sevrage éthylique, est métabolisé successivement en diéthyldithiocarbamate, puis en diéthylamine et sulfure de carbone. Le sulfure de carbone est retrouvé dans l'air expiré des malades sous traitement par le Disulfirame.

Nous avons utilisé la sepctrométrie de masse pour contrôler la compliance au traitement par Disulfirame et pour rechercher d'éventuels métabolismes anormaux de ce médicament.

Le spectre de masse montre la présence de :

	CS_2	masse 76
mais aussi de	SO_2	masse 64
et de	SO	
ou plus vraisemblablement	CH_3SH	masse 48

Le spectre de masse de l'air expiré a été réalisé systématiquement deux fois chez tous les malades traités à l'Espéral, avant traitement et après une semaine de traitement.

N. B.

Chez les malades buveurs excessifs, on retrouve toujours avant traitement un pic à la masse 46 correspondant à l'éthanol.

Parallèlement, deux groupes témoins (fumeurs et non fumeurs) non traités ont été examinés.

Ce pic a été retrouvé chez des malades supposés traités par le Disulfirame, mais chez lesquels on ne retrouvait pas les pics précédemment décrits (76-64-48), faisant ainsi la preuve de leur non respect du traitement et de la poursuite de leur intoxication éthylique.

Sulfure de carbone. Métabolisme du tétraéthylthiouram.

Chez trois malades traités par le Tétraéthylthiouram, on voit apparaître des quantités croissantes des trois métabolites principaux: CS_2-SO_2 et CH_3SH.

La cinétique d'apparition est variable selon les malades ainsi que les quantités retrouvées (figure 4 et 5).

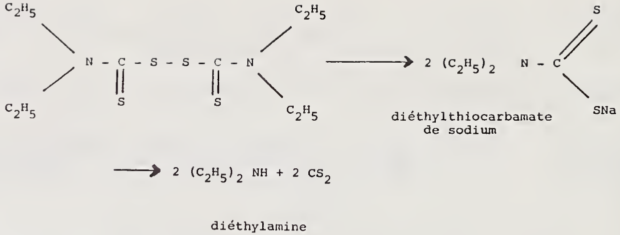


Figure 4: Metabolisme du Tétraéthylthiouram

III. Discussion

Les résultats présentés n'ont pour but que l'illustration des possibilités de détection et des limites pratiques des matériaux analytiques modernes utilisables pour les gaz et en particulier l'air expiré.

Les progrès réalisés par l'adaptation du nouveau spectrographe de masse à l'étude de l'air chez les ouvriers, se sont révélés considérables. La sensibilité de l'appareil est compatible avec les besoins de la surveillance en milieu industriel et atteint les possibilités de détection en milieu domestique contaminé.

La méthode peut certes contrôler l'atmosphère des lieux de travail, mais la détection humaine est un important apport à la démonstration d'effets toxiques potentiels dans d'autres groupes de population.

La notion de concentration physiologique en polluants gazeux dans l'air expiré est une notion illusoire.

L'utilisation de matériaux extrêmement sensibles n'est pas simple en raison de la multiplicité des composants normaux existant à très faible dose.

Dans les atmosphères urbaines, en particulier domestiques, du fait des contaminations sociales extérieures, habitudes culinaires, chauffage, fumées, par ex., en raison de :

- la persistance prolongée de produits liposolubles dans les

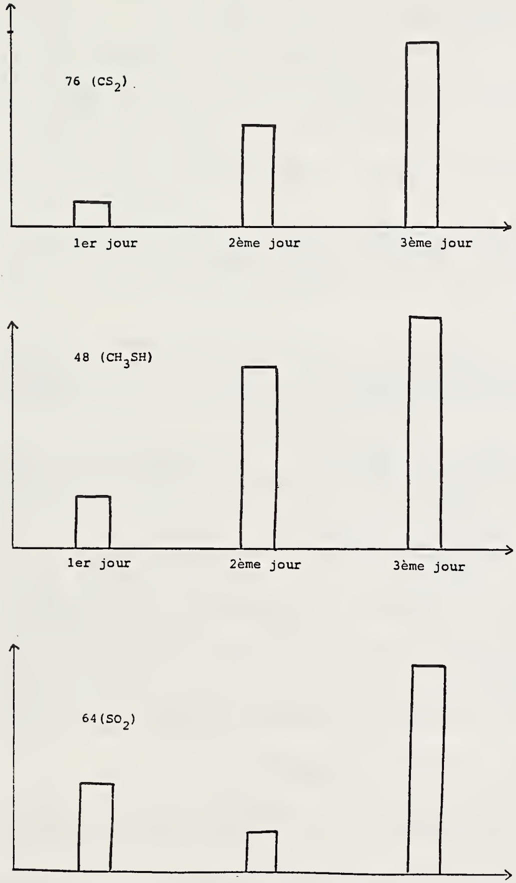


Figure 5: Unités non Définies Quantitativement Evaluation (20-30 ppb)

tissus humains en particulier les solvants chlorés dont l'élimination se prolonge à des taux de l'ordre de 1 à 10 ppb pendant des dizaines de jours.

- de l'existence de nombreux contaminants de la cavité buccale dûs aux habitudes alimentaires, alcooliques et tabagiques, de contaminants des voies aériennes en cas de tabagisme, d'alcoolisme, et d'élimination respiratoires de gaz de fermentation bactérienne (hydrogène, méthane).

- du métabolisme de xénobiotiques médicamenteux en particulier comme nous l'avons confirmé pour le tétraéthylthiouram et le sulfure de carbone.

La nécessité d'une étude clinique associée à une enquête toxicologique approfondie est indispensable pour donner un sens à des techniques analytiques sensibles à la plupart des contaminants normaux des atmosphères industrielles.

Conclusion

L'intérêt pris en France par le Ministère du Travail en raison de l'importance de la manipulation des solvants, des peintures en milieu industriel et du besoin de surveillance et de prévention des ouvriers se double de la nécessité de contrôler les manipulateurs occasionnels.

Une recherche portant sur les métabolites volatils du tétraéthylthiouram a montré la présence de sulfure de carbone dans l'air expiré de sujets traités par ce produit. La possibilité d'effets associatifs neurotoxiques entre alcool et sulfure de carbone est à indiquer.

Des recherches actuelles portent sur les effets systématiques des solvants, du sulfure de carbone et sur les effets neurocomportementaux (neurobehavorial toxicology) où les solvants (purs ou mixtes) constituent un chapître important.

Des réunions internationales vont se succéder en 1983, et l'OMS organisera une Conférence mondiale en Mai 1983 sur ce sujet (Cincinnati, USA) dans le but de sensibiliser les pays industrialisés et les pays en développement sur les risques de toxicité nerveuse et les moyens de prévention.

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LE DEVELOPPEMENT DES TESTS DE BIOTOXICOLOGIE POUR UNE MEILLEURE CONNAISSANCE DES METABOLISMES ET DES EFFETS DE SYNERGIE DES POLLUANTS CHIMIQUES

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Abstract

As an agency specializing in Occupational Health, we carry out daily, in chemical industries which call upon us, studies of the work place, evaluation of levels of chemical pollution (general atmosphere of the work place, particular jobs, individual level in workers) and we then compare the results observed with the values authorized by legislation. This well-controlled metrology allows the improvement of working conditions by limiting exposures to authorized levels, but we do not consider that this is sufficient to help prevent occupational diseases. It is absolutely necessary to consider the physicochemical, biologic, metabolic and toxicologic characteristics of pollutants when observing workers. To do that, the Occupational physician must first know the chemical form, the valence state, the granulometry which controls the metabolic behaviour, notably in the lungs, in short the toxic properties.

We are currently carrying out three types of in vitro studies involving tests which are quick, inexpensive and easy to carry out, giving important data to the Occupational physician:

- a study of in vitro solubility of dust (uranium was chosen as the focus of the test). The data we obtain with biologic liquids (from synthesis, human serum or lung specimens) allows the classification of dusts into three large categories: very diffusible (less than one day across the pulmonary wall), moderately diffusible (several weeks of settling) and hardly diffusible (at least one year retention). Throughout our studies we have also observed changes in the chemical nature and the valence state of the compounds tested, foreshadowing the metabolic phenomena likely to explain the different toxic effects of a specific pollutant.

- in vitro study of the toxic effect of gas on the pulmonary macrophages (trichloroethylene was used as the focus of the test). The macrophages are recovered by lavage of rat lung. These are cultivated and exposed to a polluted environment. The

metabolic activity of macrophages after exposure is determined by extraction and titration by chemiluminescence of adenosine triphosphate. A lowering of macrophage activity occurs for a titration of 50 ppm of trichloroethylene.

- mutagenicity studies (Ames tests - Micronucleus test - SOS repair) allow us to evaluate a mutagenic risk, either of pure products or mixtures, or of real work environments, and also the level of individual exposure using worker's urine samples.

We now have at our disposal a collection of very operational tests which, quickly and at a low cost, provide information on the metabolism, the toxic effects (chemical and mutagenic) as well as the risks of potentiation and synergy.

Résumé

Organisme spécialisé en Hygiène Industrielle, nous effectuons quotidiennement, dans les Industries chimiques qui font appel à nous, l'étude des postes de travail, l'évaluation des taux de pollution chimique (ambiance générale d'un atelier, postes particuliers, niveau individuel des travailleurs) et comparons ensuite les résultats observés aux valeurs admises par la législation. Cette méthodologie, bien maitrisée, permet d'améliorer les conditions de travail en limitant les expositions à des valeurs admissibles mais nous considérons qu'elle n'est pas suffisante pour faire progresser la prévention des maladies professionnelles. Il est absolument indispensable de tenir compte des caractéristiques physico-chimiques, biologiques, métaboliques et toxicologiques des polluants lors de la surveillance des travailleurs. Pour cela, le Médecin du Travail doit au préalable connaître la formule chimique, l'état de valence, la granulométrie qui conditionnent le comportement métabolique, notamment au niveau pulmonaire, donc les propriétés toxiques.

Actuellement, nous menons simultanément trois types d'études in vitro qui doivent déboucher sur des tests rapides, peu onéreux et faciles à mettre en oeuvre, donnant des renseignements précieux aux Médecins du Travail:

- étude de la solubilité in vitro de poussières (l'uranium a été choisi pour la mise au point du test). Les renseignements que nous obtenons avec des liquides biologiques (de synthèse, ou du sérum humain ou des broyats pulmonaires) permettent de classer les poussières en trois grandes catégories donc de prédéterminer le comportement métabolique du polluant: rapidement diffusibles (moins d'un jour) à travers la paroi pulmonaire, peu diffusible (plusieurs semaines de dépôt), très peu diffusibles (un an au minimum de rétention). Nous avons en outre observé au cours de nos études des changements de nature chimique et de l'état de valence des composés testés préfigurant

ainsi les phénomènes métaboliques susceptibles d'expliquer les différents effets toxiques d'un polluant déterminé.

- étude in vitro de l'effet toxique de gaz sur des macrophages pulmonaires (le trichloréthylène a été retenu pour la mise au point du test). Par lavage de poumon de rat on récupère les macrophages. Ces derniers sont cultivés et mis en présence d'atmosphère polluée. On détermine l'activité métabolique des macrophages après l'exposition par extraction et dosage par chimiluminescence de l'Adénosine Triphosphate. On constate ainsi une baisse de l'activité des macrophages pour une teneur en trichloréthylène de 50 ppm.

- étude de mutagénicité (tests de Ames - Micronucleus Test - SOS repair) nous permettent d'evaluer un risque mutagène soit de produits purs ou de mélanges, soit de véritables ambiances de travail, mais également le niveau d'exposition individuel par la pratique des tests sur les urines des travailleurs.

- Ainsi nous disposons à présent d'une batterie de tests, réellement opérationnels, permettant rapidement et à moindre coût, une bonne approche de la connaissance du métabolisme, des effets toxiques (chimiques et mutagènes) ainsi que des risques de potentialisation et de synergie.

Depuis plus de 20 ans, nous sommes un organisme spécialisé en Hygiène et Sécurité Industrielle:

- Nous avons acquis une expérience certaine dans la surveillance des travailleurs et des conditions de travail de l'Industrie Nucléaire et plus particulièrement de l'Uranium.

- En outre, sur le plan théorique, nous suivons l'évolution de la pensée scientifique et des concepts dans le domaine de la radioprotection générale.

- Enfin nous intervenons, selon la demande, à l'échelon national, dans l'industrie non nucléaire (industrie chimique, électronique, métallurgie etc.) pour évaluer les risques de l'exposition des travailleurs à des polluants professionnels.

- C'est ainsi que, notamment, nous déterminons les taux de pollution chimique dans les ambiances générales, à des postes particuliers, ou au niveau des voies respiratoires des travailleurs.

- Nous évaluons la contamination interne par le dosage des toxiques ou des métabolites dans le sang, les urines, les cheveux, les selles etc.

- Nos résultats sont ensuite comparés aux valeurs admises par la législation. Cette méthodologie bien maitrisée permet d'améliorer les conditions de travail en limitant les expositions et en améliorant la ventilation, les aspirations etc.

Nécessité de tests de biotoxicologie

Mais cette façon de concevoir l'Hygiène Industrielle n'est pas suffisante pour faire progresser la prévention des maladies professionnelles. Il est en effet absolument indispensable de tenir compte des caractéristiques physico-chimiques, biologiques, métaboliques et toxicologiques des polluants chimiques lors de la surveillance des travailleurs. Pour cela, le Médecin du Travail doit au préalable être en possession des renseignements suivants:

- Formule chimique et état de valence des composés manipulés - une enquête auprès des services de production lui fournira ces renseignements.

- Granulométrie des aérosols - les techniques de mesure sont bien au point et ne posent pas de difficultés aux Laboratoires d'Hygiène Industrielle spécialisés.

Rappelons que la forme chimique, l'état de valence et la granulométrie vont conditionner le métabolisme de la particule au niveau des bronches pulmonaires (phénomènes de rétention et d'épuration) donc des propriétés toxiques.

Ces renseignements ne nous paraissent pas encore suffisants car ils ne peuvent pas à eux seuls préjuger du comportement du toxique dans l'organisme. Notre expérience, acquise en Hygiène Industrielle dans le secteur nucléaire, nous conduit à recommander la mise en oeuvre de tests de biotoxicologie pour une meilleure connaissance des métabolismes et des effets de synergie des polluants chimiques entre-eux.

Dans le Service d'Hygiène Industrielle à Pierrelatte, nous développons actuellement 3 types d'études in vitro qui débouchent sur des tests rapides, peu onéreux, faciles à mettre en oeuvre et susceptibles de donner des renseignements précieux aux Médecins du Travail.

Ce sont:

- Etude de solubilité in vitro de poussières;

- Etude in vitro de l'effet toxique de gaz sur des macrophages pulmonaires;

- Etudes du pouvoir mutagène sur les produits d'usage industriel, les ambiances de travail, les urines des travailleurs.

Etudes 'In Vitro' de la solubilité des poussières

Objectifs de l'étude

Considérant les concepts admis dans le domaine nucléaire concernant les différences de comportements métaboliques d'un radiotoxique selon sa formule chimique de présentation (Nitrate, Fluorure, Oxyde, etc.), nous avons pensé qu'il devait en être de même pour les toxiques chimiques non radioactifs.

Il est en effet admis universellement, dans le domaine nucléaire, que les radiotoxiques se classent en 3 grandes catégories selon leur plus ou moins grande rapidité de passage au travers de l'alvéole pulmonaire:

- Composés transférables (Classe D) - le passage s'effectue au cours des premières 24 heures qui suivent l'inhalation.
- Composés moyennement transférables - (Classe W) le passage à travers la paroi alvéolaire nécessite plusieurs semaines. On dit que la période biologique (temps nécessaire pour que la moitié de la quantité présente à l'origine soit éliminée) est de 50 jours.
- Composés peu transférables - (Classe Y) dont la période biologique d'épuration est évaluée à 500 jours.

Cette classification a été établie sur la base des expériences animales effectuées avec des radiotoxiques inhalés sous différentes formes chimiques (oxyde, fluorure, nitrate, etc.) ou des observations humaines après contaminations accidentelles. On connaît donc, en principe, le comportement previsionnel de chaque composé.

Mais nous avons considéré que, dans la réalité industrielle, la nature chimique des composés susceptibles d'être inhalés n'était pas toujours connue de façon absolue ou rigoureuse, qu'il pouvait exister des mélanges de composés de nature chimique différente, que les conditions de fabrication ou de traitement de ces composés pouvait influer sur le comportement biologique (la température de fabrication des oxydes notamment). Pour ces différentes raisons nous avons considéré qu'il serait fort utile de disposer d'un test in vitro, rapide à mettre en oeuvre permettant d'évaluer la "solubilité" des agents chimiques présentes dans une atmosphère de travail industrielle. Si l'on connait par ailleurs la concentration du toxique dans cette atmosphère, on peut alors beaucoup mieux cerner les risques potentiels aux-quels sont exposés les travailleurs, déterminer les conditions de surveillance toxicologique (choix du meilleur prélèvement biologique: sang, urine, selles, et de la meilleure époque du prélèvement par rapport à l'exposition) définir les "valeurs limites" à l'excrétion de ces toxiques dans les prélèvements biologiques.

Sur ces bases, nous avons entrepris la mise au point d'un test de détermination in vitro de la solubilité des poussières. Nous avons pratiqué nos essais avec l'Uranium naturel sous différentes formes chimiques pour cette mise au point.

Rappelons que nous connaissons par ailleurs dans la classification admise dans le domaine nucléaire, le comportement théorique de chaque composé chimique de l'Uranium:

- Oxyfluorure (UO2 F2) et nitrate d'uranyle sont de la Classe D (T biologique = 1 jour).
- Tétrafluorure, trioxyde, peruranate, Carbonate sont de la Classe W (T biologique = 50 jours).
- Dioxyde UO2 et oxyde U308 sont de la Classe Y (T biologique = 500 jours).

Ces renseignements devaient nous permettre d'étalonner ou de codifier nos conditions expérimentales en comparant les résultats obtenus par notre test in vitro aux données de la littérature obtenues par expérimentation animale ou observations des contaminations humaines accidentelles.

Matériel et méthodes

La Figure 1 décrit le montage utilisé.

- Dans une cellule en plexiglass de diamètre 37 mm on introduit, entre deux membranes Millipore de porosité 0,22 u, un sandwich de poussières; on mesure le poids et la surface du dépôt et la granulométrie et les caractéristiques chimiques des poussières.
- Les poussières sont léchées par un liquide biologique synthétique (solution de Gamble) dont la composition, indiquée dans le Tableau 1, est similaire à celle du liquide interstitiel pulmonaire. Ce liquide, pulse par une pompe péristaltique avec un débit de 0,1 ml/min, est réchauffé à 37°C dans un bain-marie avant de passer dans la cellule, celle-ci étant elle-même immergée dans ce bain-marie.
- A la sortie de la cellule, on récupère par un collecteur de fractions la solution de léchage en vue de l'analyse.

Application à différents composés d'uranium naturel: resultats et commentaires

Dans le cadre de la surveillance d'une usine de traitement de composés uranifères le Médecin du Travail avait constaté que l'excrétion de l'Uranium dans les urines des travailleurs ne correspondait pas à ce que l'on était en droit d'attendre pour un composé moyennement transférable (Tétrafluorure d'uranium - UF_4).

Nous avons mis en oeuvre la technique décrite ci-dessus. Les caractéristiques des poussières étudiées étaient les suivantes:

- La granulométrie mesurée à l'aide du Cascade Impactor Andersen est D 50% = 4,7 μ.

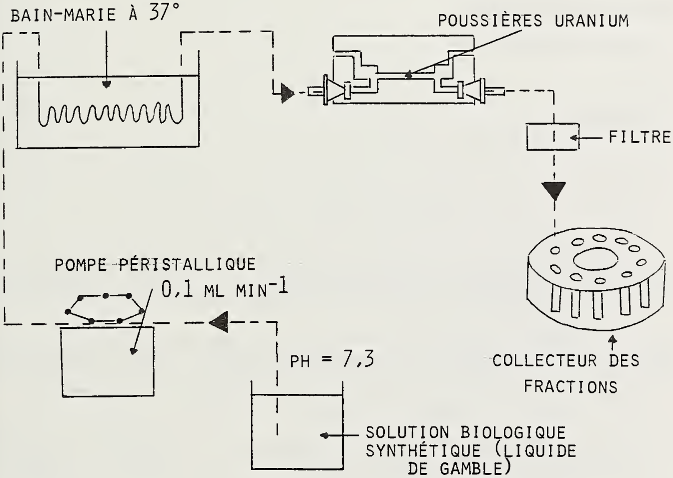

Figure 1: Schéma Expérimental pour Déterminer in Vitro la Solubilité de Poussières

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- Ces caractéristiques chimiques ont été déterminées par spectre d'émission X, ce qui permet d'obtenir le spectre des éléments simples présents, par spectrographie aux rayons X, par spectrographie ESCAE qui permet d'étudier la structure ionique de la poussière (Figures 3-4).

TABLEAU 1: Composition de la Solution de Gamble

Produit	Concentration en mmole^{-1}
Chlorure de sodium	116
Chlorure d'ammonium	10
Bicarbonate de sodium	27
Phosphate monosodique	1.2
Citrate trisodique	0.2
Glycine	6
L-cystéine	1
Chlorure de calcium	0.2
Sterlane	250

Nous avons dosé par fluorimétrie, dans les différentes fractions recueillies, l'uranium dissous dans la solution de Gamble en fonction du temps.

La figure 2 rassemble les résultats obtenus sur environ 50 essais. Elle indique en fonction du temps l'évolution de la dissolution de l'Uranium en % Uranium cumulé.

Les résultats obtenus étaient les suivants:

- L'UF4 ne semble pas se comporter comme un composé moyennement transférable (classe W) mais comme un composé peu transférable (classe Y).
- Il y a transformation chimique de l'UF_4 en un composé oxydé. La figure 3 montre une modification de l'environnement électronique de l'Uranium donc transformation chimique de l'échantillon. La figure 4 montre la disparition de fluorures et l'apparition d'oxygène.

Nous avons effectué d'autres expériences avec d'autres composés d'uranium - nitrate d'uranyle, oxyfluorure d'Uranium, Oxydes (UO3 ; U308).

Les résultats des différents essais obtenus sont rassemblés dans le Tableau 2 et la figure 5.

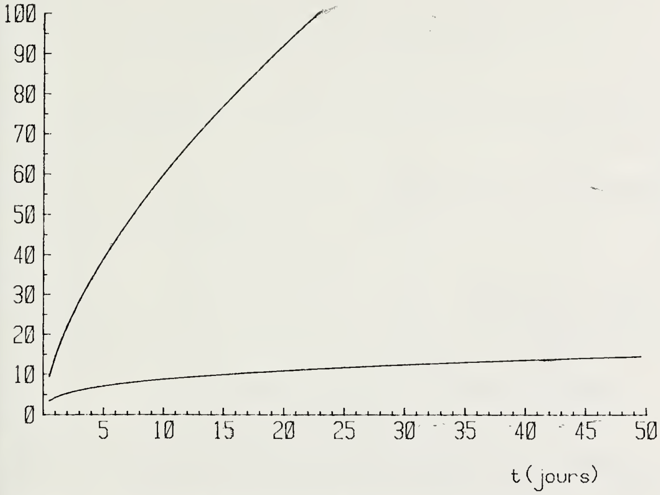


Figure 2: Courbe de Solubilité Uranium et Flourure

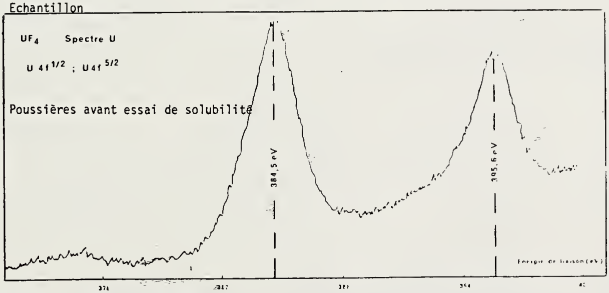
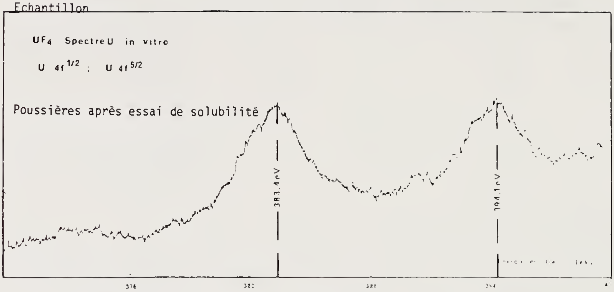


Figure 3: Spectres Escae



La comparaison de ces spectres met en évidence la transformation chimique de l'UF4

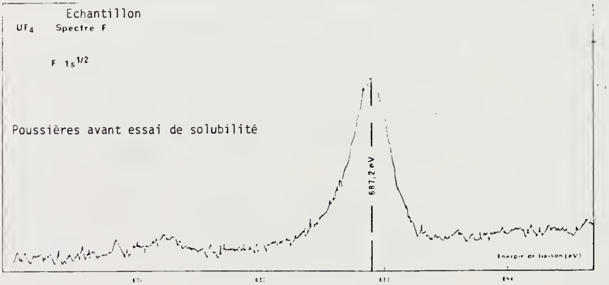


Figure 3: (con't) Spectres Escae

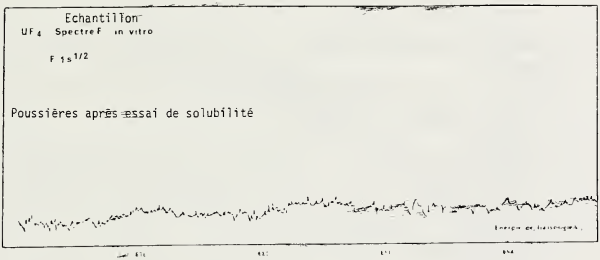


Figure 4: La Comparaison de Ces Spectres Met en Evidence la Disparition de Fluorures Lors des Essais de Solubilité

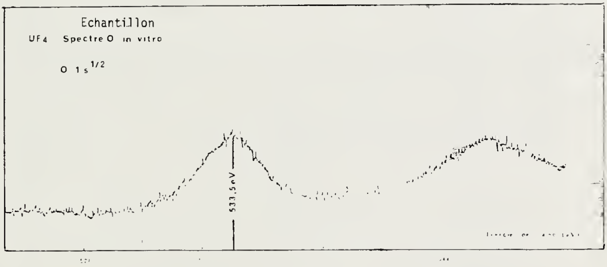
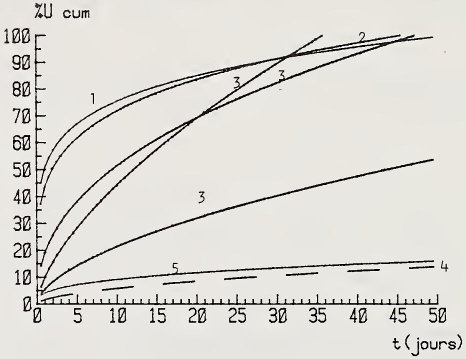


Figure 4: (con't) Mise en Evidence d'Apparition d'Oxygène dans les Poussières après les Essais de Solubilité



1 - Courbe du $UO_2(NO_3)_2$, $6H_2O$ atteignant rapidement 100 % (1 à 2 j)

2 - Courbe du UO_2F_2 " " " (1 à 2 j)

3 - Courbes plus dipersées de UO_3 (à étudier plus précisément)

4 - Courbe de U_3O_8

5 - Courbe de UF_4 ressemblant beaucoup à U_3O_8

Figure 5: Solubilité Comparée Eléments Class D.W.Y.

TABLEAU 2: Resultats Obtenus au Cours de nos Différents Essais de Détermination in Vitro de la Solubilité de Poussières

CLASSE	ELEMENT	n°	Pp	PU	MODELE REGRESSION	t50%	t100%
D	$UO_2(NO_3)$ $6H_2O$	1	9,6 mg	4,5 mg	$y = 50,58\ t^{n}\ 0,173$	0,9 j.	51,4 j
		2	10 mg	4,7 mg	$y = 41,73\ t^{n}\ 0,229$	2,2 j.	45,4 j
		3	21,1 mg	10 mg	$y = 57,11\ t^{n}\ 0,151$	0,4 j.	40,8 j
	UO_2F_2	4	9,5 mg	7,3 mg	$y = 47,65\ t^{n}\ 0,193$	1,3 j.	46,6 j
		5	5,8 mg	4,5 mg	$y = 43,18\ t^{n}\ 0,220$	1,9 j.	45,5 j
		6	13 mg	10 mg	$y = 39,05\ t^{n}\ 0,250$	2,7 j.	43 j
W	UO_3	7	11 mg	9,1 mg	$y = 19,14\ t^{n}\ 0,429$	9,4 j.	47,2 j
		8	26 mg	21,6 mg	$y = 10,14\ t^{n}\ 0,640$	12,1 j.	35,7 j
		9	12 mg	10 mg	$y = 5,69\ t^{n}\ 0,576$	43,4 j.	144,5 j
Y	U_3O_8	10	23 mg	19,5 mg	$y = 1,40\ t^{n}\ 0,573$	512 j.	-
		11	10 mg	8,5 mg	$y = 1,67\ t^{n}\ 0,541$	535 j.	-
		12	12 mg	10,1 mg	$y = 1,89\ t^{n}\ 0,452$	1393 j.	-
	UF_4	13	10 mg	7,6 mg	$y = 5,02\ t^{n}\ 0,313$	1546 j.	-
		14	11,6 mg	8,8 mg	$y = 4,69\ t^{n}\ 0330$	1302 j.	-
		15	20 mg	15,2 mg	$y = 4,16\ t^{n}\ -,345$	1349 j.	-

Conclusion

Nous disposons à présent d'un test permettant de déterminer in vitro la solubilité de poussières inhalées par un travailleur. On peut ainsi prédire la durée de rétention au niveau de l'alvéole, le métabolisme, et l'excrétion du composé toxique.

Etude In Vitro de l'effet toxique de gaz sur des macrophages pulmonaires

Objectifs de l'étude

Les effets à long terme de la pollution chimique de l'atmosphère de travail, les relations dose-effet doivent être étudiées pour une bonne prévention.

Mais la complexité des effets dûs à d'éventuels mélanges de polluants, pouvant provoquer des synergies ou des potentialisations, nous a paru nécessiter la mise au point d'un test global de l'effet de l'exposition à des gaz toxiques.

Nous avons retenu pour cela les macrophages pulmonaires qui jouent un rôle important lors de l'inhalation de toxiques chimiques, puisqu'ils participent à l'épuration du milieu alvéolaire par les phénomènes de phagocytose et pinocytose.

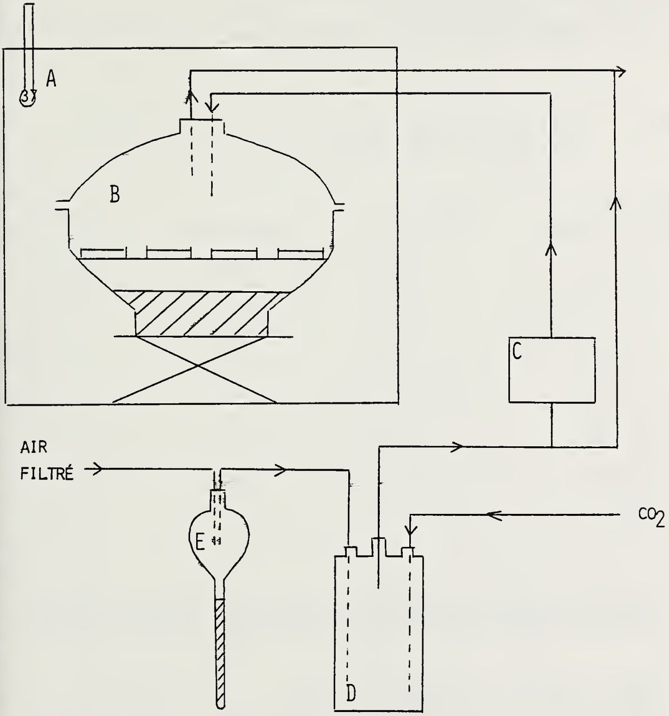
Matériel et méthodes

Macrophages alvéolaires - Ils sont récoltés chez des rats mâles, de race Sprague Dawley, par lavage bronchopulmonaire. La suspension cellulaire obtenue contient en moyenne 10^7 macrophages alvéolaires qui sont soumis à une sélection par adhérence au verre. Puis ils sont mis en survie en boite de Pétri.

Conditions d'exposition des macrophages - L'exposition est réalisée dans une enceinte à 37°, dont l'atmosphère saturée en vapeur d'eau contient 5% d'anhydride carbonique (figure 6).

Exposition - Immédiatement après leur mise en survie en phase gazeuse, les macrophages sont placés à l'étuve pendant au moins 4 heures. Un lot est alors placé dans l'atmosphère à tester qui contient une concentration connue du gaz que l'on veut étudier tandis qu'un autre lot est conservé comme témoin.

Mesure des effets - Après l'exposition, on mesure la teneur en ATP (Adénosine Triphosphate) par bioluminescence après extraction par une solution aqueuse de diméthylsulfoxyde.



- A = Etuve thermostatée à 37°C
- B = Enceinte dans laquelle sont exposés les macrophages
- C = Pompe à débit constant (30 l/h)
- D = Enceinte de mélange
- E = Ampoule contenant le solvant à tester

Figure 6: Système d'Exposition des Macrophages à une Atmosphère Toxique

Essais pratiques - Resultats et commentaires

Nous avons pratiqué des essais avec du trichloroéthylène. Nous obtenons les résultats regroupés dans le tableau 4.

TABLEAU 4: Essais de Cytotoxicité du Trichloroéthylène sur Microphages Pulmonaires

Concentration Trichloréthylène	Index de (1) Cytotoxicité	Moyenne (%)	Ecart-Type
50 ppm	0.25.39.49	28.25	21
100 ppm	16.26.31.38	27.75	9
150 ppm	22.39.43.55	39.75	13
500 ppm	38.43.54.65	50	12
1000 ppm	31.52.58.67	52	16
1500 ppm	57.60.64.66	61.7	4
2000 ppm	52.58.67.73	62.5	9

(1) Index de cytotoxicité = différence mesurée entre la quantité d'ATP dosée dans les macrophages témoins et celle dosée dans les macrophages exposés exprimée en pourcentage.

Pour chaque concentration en trichloroéthylène, 4 expériences ont été réalisées. Les résultats sont indiqués dans la colonne "Index de Cytotoxicité". La moyenne et l'écart-type sont calculés sur ces 4 expériences (figure 7).

Essais de cytotoxicité du trichloréthylène sur macrophages pulmonaires

- Pour des concentrations en trichloroéthylène inférieures à 50 ppm (0,26 mg/litre d'air), il n'a pas été mis en évidence d'action cytotoxique nette.

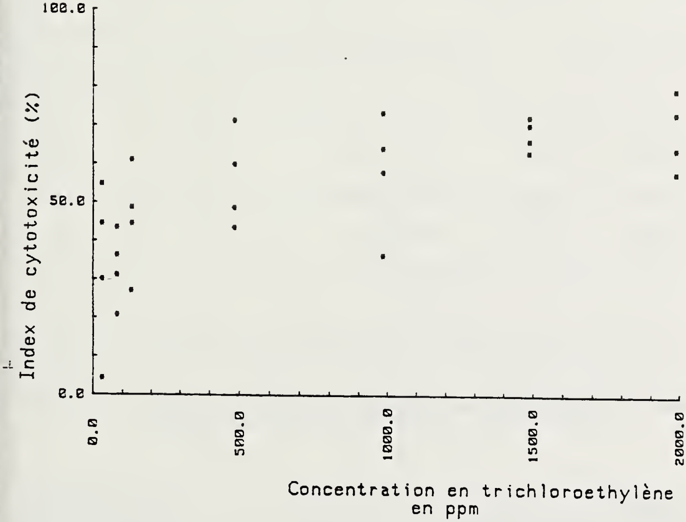


Figure 7: Cytotoxicité du Trichloroéthylène

Les macrophages sont exposés pendant 7 heures à une atmosphére contenant une quantité connue de trichloroéthylène. Puis leur concentration intracellulaire en ATP est comparée à celle de macrophages témoins provenant du même lot.

Nous avons choisi d'étudier le dioxane car c'est un additif du trichloréthylène technique.

Pour chaque concentration en dioxane, 4 expériences ont été réalisées.

Pour chaque expérience, la quantité d'ATP moyenne a été calculée sur des lots de 5 boites contenant chacune 10^6 macrophages. Les résultats sont regroupés dans le Tableau 5.

TABLEAU 5: Essais de Cytotoxicité du Dioxane sur Macrophages Pulmonaires

Concentration dioxane	Index de cytotoxicité %	Moyenne %	Ecart-type
130 ppm (0.54 mg/l)	0-0-12-15	9.25	11.9
380 ppm (1.6 mg/l)	25-33-35-38	32.75	5.5
760 ppm (3.2 mg/l)	42-50-54-62	52	8.3
1900 ppm (7.9 mg/l)	66-81-90-91	82	11.5

On constate un effet cytotoxique du dioxane vis à vis des macrophages alvéolaires de rats.

La cytotoxicité du dioxane vis à vis des macrophages augmente avec la concentration suivant une loi:

$$Y = A + B \text{ Log } x \quad (r = 0.989)$$

Nous avons ensuite étudié les effets de potentialisation du mélange trichloroéthylène et dioxane. Les résultats sont regroupés dans le Tableau 6.

Les macrophages ont été exposés pendant 7 heures dans une atmosphère chargée en dioxane.

Puis la concentration en ATP des macrophages exposés est comparée à celle de macrophages témoins appartenant au même lot.

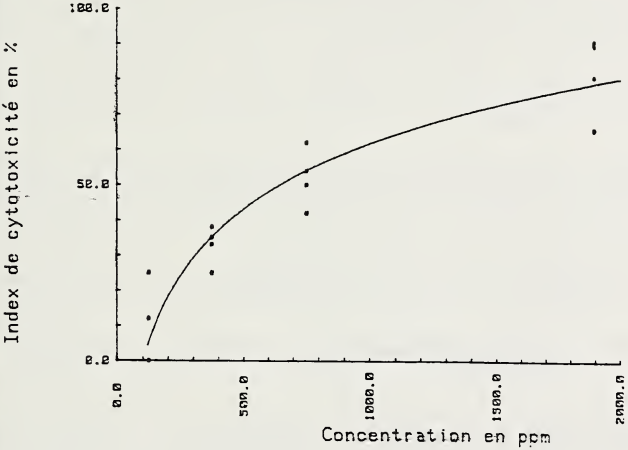


Figure 8: Cytotoxicité du Dioxane

TABLEAU 6: Essais de Potentialisation de l'Effet Cytotoxique de Mélanges de Trichloroéthylène et de Dioxane

CONCENTRATION DE TRICHLOROETHYLENE ET DE DIOXANE	ATP DES TEMOINS ng/10^6 cell.	ATP EXPOSES ng/10^6 cell	INDEX DE CYTOTOXICITE
- Trichloroéthylène 2000 ppm - Dioxane 760 ppm	1289 ± 117	592 ± 61	54 %
- Trichloroethylène 2000 ppm - Dioxane 760 ppm	941 ± 84	364 ± 42	60 %
- Trichloroéthylène 2000 ppm - Dioxane 760 ppm	1518 ± 143	531 ± 77	65 %

Chaque point représente la moyenne de 5 boites contenant chacune 10^6 macrophages appartenant au même lot.

Les index de cytotoxicité obtenus sont à rapprocher de ceux obtenus avec le dioxane seul = il n'y a donc aucun effet de potentialisation de la toxicité.

Les essais effectués montrent que la sensibilité de la méthode utilisée permet d'observer un effet cytotoxique pour des valeurs inférieures à la concentration maxima admissible dans le cas du trichloroéthylène

En effet, on observe une diminution de la quantité d'ATP de 28% après exposition à 50 ppm de trichloroéthylène alors que la concentration maxima admissible est de 100 ppm.

Nous avons étudié la SOLVESSO qui est une coupe pétrolière utilisée dans des procédés d'extraction.

Le Tableau 7 et la figure 9 indiquent les résultats obtenus pour différentes concentrations de SOLVESSO.

TABLEAU 7: Essais de Cytotoxicité du SOLVESSO sur Macrophages Pulmonaires

CONCENTRATION EN SOLVESSO en ppm	% CYTOTOXICITE	CONCENTRATION EN SOLVESSO en ppm	% CYTOTOXICITE
550	0	1100	83
800	18	1150	96
850	28	1666	77
878	32	1704	86
916	32	2033	100
1100	83		
1145	84		

Conclusion

Le test utilisé apporte des informations dans deux domaines:

- Cytotoxicité des gaz au sens strict du terme.
- Effet de ces gaz sur l'appareil respiratoire.

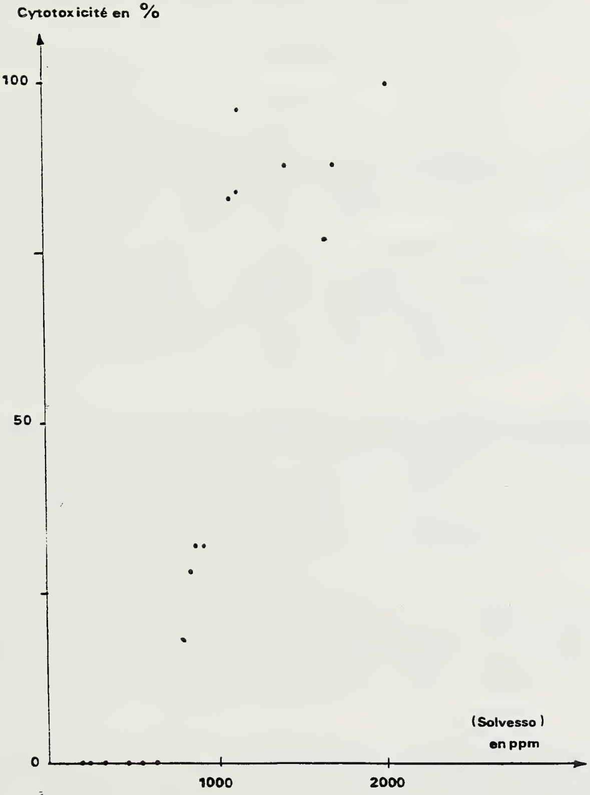


Figure 9: Cytotoxicité du SOLVESSO

Par ailleurs, il permet d'étudier les effets de potentialisation de plusieurs polluants dans des conditions expérimentales strictement contrôlées.

C'est un test qui maintenant est parfaitement opérationnel grâce aux essais que nous avons pratiqué sur différents gaz à différentes concentrations.

Mise en évidence de l'effet mutagene

Objectifs de l'étude

La mise en évidence d'un risque cancérigène est longue et onéreuse; elle s'effectue sur des grands lots d'animaux. Or on sait qu'une substance mutagène provoque des perturbations au niveau de l'ADN pouvant créer un processus cancérigène; on peut, par extrapolation, admettre qu'un produit à effet mutagène est susceptible d'avoir un pouvoir cancérigène.

La mise en évidence d'un effet mutagène peut s'effectuer par des tests in vitro, rapides à mettre en oeuvre et peu onéreux, par comparaison avec la recherche du pouvoir cancérigène. Nous avons codifié une batterie de tests qui permet la mise en évidence de l'effet mutagène.

Matériel et méthodes

Nous avons codifié les tests suivants:

Test d'Ames avec des souches mutantes de *Salmonella typhimurium*. Les souches bactériennes utilisées présentent la particularité d'être incapables de synthétiser une enzyme nécessaire à la fabrication de l'histidine, indispensable à leur développement. Un agent mutagène peut induire une mutation de ces bactèries (mutations revertantes) qui, revenant ainsi à leur état primaire, sont alors capables de croître sur un milieu dépourvu d'histidine.

Le nombre de bactéries ayant ainsi muté est capable de croître en colonies en milieu dépourvu d'histidine. Ceci est caractéristique du pouvoir mutagène de l'agent chimique étudié. Il arrive souvent que ce soient les métabolites de l'agent chimique qui se révèlent actifs. C'est la raison pour laquelle on ajoute aux préparations des enzymes d'extrait d'homogénat de foie de rat pour assurer la métabolisation.

Test du micronucleus

Il permet de mettre en évidence la mutation chromosomique. On utilise des souris auxquelles on administre le produit à étudier solubilisé par voie intrapéritonale ou "per os" ou par inhalation le gaz ou l'aérosol à tester. Trente heures après l'intoxication les animaux sont sacrifiés, on effectue un prélèvement de la moelle osseuse du fémur.

Sur l'étalement on recherche la présence de micronoyaux (corps de Howell Jolly) dans les erythrocytes polychromatiques.

L'intérêt de ce test est de travailler sur des cellules eucaryotes.

Test S.O.S. Repair (S.O.S. chromotest inductest colorimétrique).

L'étude du mécanisme de réparation de l'ADN est étudié sur bactérie (Eschérichia coli PQ37).

Les différentes lésions de l'ADN provoquées en particulier par l'exposition à certaines substances chimiques sont: la coupure de l'une des 2 chaînes de l'ADN, l'enlèvement d'un fragment d'une des chaînes et la création de liaisons anormales entre les bases, sous-éléments de l'ADN.

Un des systèmes de réparation de l'ADN est placé sous le contrôle d'une protéine appelée Rec A. La synthèse de cette protéine est induite dans la bactérie, lorsque le système ordinaire de réparation de l'ADN est déborde à cause de la présence de trop nombreuses lésions. Le Rec A agit par clivage sur certains répresseurs de gêne pour libérer l'action S.O.S.: action enzymatique dans le système réparateur de l'ADN.

Applications

Nous avons pratiqué ces 3 tests sur différents milieux ou produits replacés dans leurs conditions réelles d'utilisation:

- goudron de revêtement de route porté à différentes températures (250°-350°-550°).
- encre d'imprimante d'ordinateur;
- Benzo-à-Pyrène, Benzène inhalés par des souris;
  Urines de travailleurs exposés à des produits mutagènes.

Resultats obtenus - et commentaires

Sur le goudron porté à différentes températures on a constaté qu'il existait à 550° un pouvoir mutagène faible, ce résultat n'est pas surprenant car au-dessus de 450° il se libère des hydrocarbures polycycliques (HPA) aromatiques. Il existe, à 250°C, un pouvoir mutagène discret, sans doute dû à d'autres composés que les H.P.A.

Les vapeurs de goudron surchargées de quantités constantes de Benzo-à-Pyrène, ou d'aminoanthracène, ou de nitrofluorène ou de méthyl méthane sulfonate (substances connues pour avoir un effet mutagène) ont révélé une potentialisation de leurs effets mutagènes avec le Benzo-à-Pyrène et le 2 aminoanthracène.

Nous avons mis en évidence qu'une encre d'imprimante d'ordinateur portée à sa température d'utilisation émettait des vapeurs et aérosols présentant un pouvoir mutagène. Par la suite nous avons testé les différents composants de cette encre pour déterminer le produit responsable de cette mutagénicité, ce qui a permis de remplacer ce composant dans la formulation industrielle par un autre produit.

Lors de la surveillance de travailleurs exposés à des produits mutagènes, nous avons pu mettre en évidence les mauvaises conditions de travail d'ouvriers d'entretien dont les urines, recueillies 24 heures après leur intervention sur des machines, montraient un pouvoir mutagène significatif. A signaler que dans le cas des urines il faut tenir compte du facteur: fumeur, non fumeur.

Conclusion

Cette batterie de 3 tests (Test de Ames, Micronucléus, SOS Repair) nous permet une bonne approche du risque mutagène dû à l'emploi de certains produits à usage industriel, utilisés purs ou en mélanges, et replacés dans leurs vraies conditions d'utilisation. Elle nous permet également de contrôler les ambiances de travail en les appliquant aux atmosphères prélevées dans les entreprises. Enfin, elle permet d'évaluer le niveau individuel d'exposition des travailleurs par la pratique des tests sur les urines.

Ils permettent donc d'améliorer les conditions de travail et la prévention des risques mutagènes.

Conclusion générale

Nous disposons à présent d'une batterie de tests, réellement opérationnels, permettant, rapidement et à moindre coût, une bonne approche de la connaissance du métabolisme, des effets toxiques (chimiques et mutagènes) ainsi que des risques de potentialisation et de synergie des polluants chimiques professionnels.

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PERIPHERAL SENSORY IRRITATION AS A FACTOR IN DEFINING WORKPLACE EXPOSURE GUIDELINES

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Abstract

Peripheral sensory irritant materials interact with sensory receptors in exposed body surfaces, producing discomfort at the contaminated site with local and systemic reflexes. For occupational exposure considerations the principal sites are the eye and respiratory tract. Exposed workers experience discomfort with blepharospasm, excess lachrymation, cough, rhinorrhoea, and altered breathing pattern. Systemic effects may include transient elevation of blood pressure with bradycardia. The bioprotective effects, warning of potentially harmful materials in the atmosphere, are detrimental to safe and efficient working. Also, sensory irritant effects often occur at concentrations lower than those causing injury by acute or short-term repeated exposure. Thus, a knowledge of sensory irritant effect levels is of considerable assistance in defining safe working conditions. Sensory irritation can be studied in laboratory animals by various approaches, including detection of blepharospasm, neurophysiological measurements on supraorbital nerve activity, and by determining the depression of respiratory rate by stimulation of nasal mucosa or pulmonary sensory receptors. In man it is possible to assess concentrations at which sensory irritant sensations occur. Determining the difference in concentrations between those producing threshold sensory irritant effects and those causing tissue injury indicates the margin of safety produced by a sensory irritant response. The presentation will discuss: the basis for using sensory irritancy for defining exposure guidelines, quantitative determination of sensory irritant potential, factors influencing the response, and the relevance of animal studies to workplace exposure.

Résumé

Les substances irritant le système sensoriel périphérique réagissent avec les récepteurs sensoriels des surfaces exposées du corps, perturbant à l'endroit contaminé les réflexes locaux et systémiques. Les principaux endroits vulnérables en milieu de travail sont les yeux et les voies respiratoires. Les travailleurs exposés ressentent des malaises causés par le blépharospasme, une production lacrymale excessive, la toux, la rhinorrhée et un rythme respiratoire modifié. Les effets

systémiques peuvent comprendre une élévation intermittante de la pression sanguine avec bradycardie. Les effets bioprotecteurs et les avertissements concernant les substances potentiellement dangereuses dans l'atmosphère sont nuisibles au travail sécuritaire et efficace. De plus, les effets des irritants sensoriels se produisent souvent à des concentrations inférieures à celles causant des lésions par des expositions aigues ou répétées à court terme. La connaissance des concentrations de substances ayant un effet irritant sensoriel est donc très utile pour définir des conditions de travail sécuritaires. L'irritation sensorielle peut être étudiée chez des animaux en laboratoire à l'aide de diverses méthodes, y compris la détection du blépharospasme, les mesures neurophysiologiques de l'activité du nerf supraorbital, et l'évaluation de la dépression du taux respiratoire par stimulation de la muqueuse nasale ou des récepteurs sensoriels pulmonaires. Chez l'homme, il est possible d'évaluer les concentrations aux quelles se produisent des sensations d'irritation sensorielle. La mesure de la différence entre les concentrations qui produisent les effets seuils d'irritation sensorielle et celles qui causent les lésions tissulaires indique la marge de sécurité produite par une réaction à l'irritation sensorielle. La présentation traitera des points suivants: la justification d'une utilisation de l'irritation sensorielle pour dèfinir les normes d'exposition, la détermination quantitative du potentiel d'irritation sensorielle, les facteurs influant sur la réaction, et la pertinence des études effectuées sur des animaux, extrapôlées à l'exposition en milieu de travail.

Introduction

Quantitative exposure guidelines are required to ensure the best possible protection against adverse effects from substances dispersed in the atmosphere. The development of such exposure guidelines requires information relating not only to the production of effects detrimental to health, but also pharmacological effects such as narcosis and irritation. Thus, there is a need to review information derived from many disciplines and sources; these include toxicology, epidemiology, occupational medicine, industrial hygiene surveys, and in-use considerations. When extensive information is available, certain specific toxic effects may assume a dominant role in defining exposure guidelines; for example, oncogenicity, non-neoplastic chronic toxicity, adverse reproductive effects and teratogenicity. With substances for which there is a deficiency of information on toxicity, the known irritancy of a material may be a primary or significant determinant of exposure guidelines, and in particular for assigning an upper permissible level of exposure.

In general, the basis for the development of exposure guidelines is related to the types of effect noted. Thus, a time-weighted average value is usually based on information on repeated exposure toxicity. The short-term exposure limit is applied to situations where toxic effects are likely to occur by exposure to high concentrations of a substance by brief exposure. The ceiling concept, which is a concentration not to be exceeded, even momentarily, is applied where substances produce potentially harmful effects which are rapid in onset following exposure. The ceiling limit will therefore apply, amongst other considerations, to pharmacological or exaggerated physiological responses; peripheral sensory irritancy is an example. The relative importance of irritation as a factor in defining exposure guidelines is indicated by the fact that of the approximately 600 entries in the current documentation for values advised by the American Conference of Governmental Industrial Hygienists (1983), irritation is a significant factor in assigning values in 17% of the entries.

Nature of sensory irritant responses

The word 'irritancy' is used somewhat loosely to describe two types of local response to chemicals, one being pathological, and the other physiological.

Primary irritants cause local acute inflammation following the contamination of a body lining or covering membrane (ie. mucosa or skin).

Peripheral sensory irritants interact with sensory nerve receptors in skin and mucosa at the site of contamination, and cause local reversible sensations of pain or discomfort, with associated reflexes which may be local and/or systemic (Figure 1). Thus, the major characteristic features of peripheral sensory irritants are:

i. They act locally; ie. at the site of contamination of skin or mucosa.

ii. They stimulate sensory nerve receptors and produce a local discomfort with locally mediated reflexes.

iii. There may be associated systemic reflexes, usually autonomic in type.

In general, sensory nerve fiber receptors react nonspecifically to chemical peripheral sensory irritants, and the term "common chemical sense" has been used to differentiate this primary sensory function from the chemically-induced specific sensations of taste and smell (Keele, 1962). Most, but not all, substances which cause inflammation will also act as peripheral sensory irritants. In such cases the sensory irritant response is usually produced at exposure concentrations significantly lower than those which cause inflammatory change. In this respect, peripheral sensory irritant effects warn of the presence of potentially tissue injuring substances.

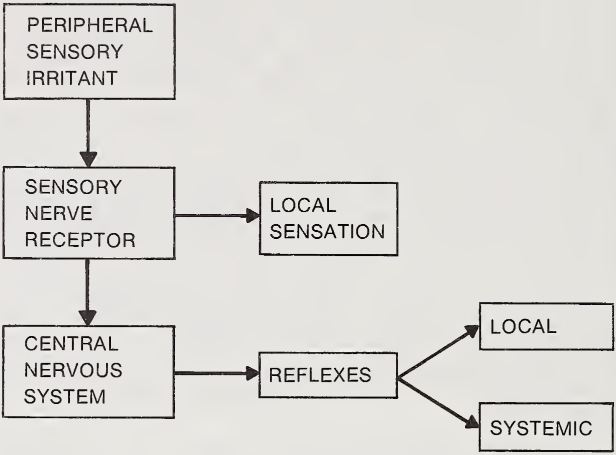

Figure 1: Schematic Respresentation of Effects Produced by Peripheral Sensory Irritant Materials

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The chemicals that are capable of inducing peripheral sensory effects are of widely differing structures, and the mechanisms by which they produce their effects are lacking detail. There are no identifiable specific morphological receptors. It is known that the sensitivity of receptors to peripheral sensory irritants is apparently related to their normal physiological function (Green and Tregear, 1964). In skin, irritants appear to be selective in that they excite only polymodal nociceptors and warm thermoreceptors (Foster and Ramage, 1981). Experimental studies indicate that peripheral sensory irritant materials combine with membrane-associated binding sites, and the binding affinity is a factor in determining the potency of the irritant (Green et al., 1979). In some instances these may be in association with sulphydryl or amino groups of membrane proteins or enzymes (Dixon and Needham, 1946; Silver et al., 1967). Douglas (1981) has reviewed the mechanisms of sensory irritation.

The major sites at which peripheral sensory irritant effects can be produced are the eye, skin and respiratory tract. With respect to the development of occupational exposure guidelines, eye and respiratory tract are the more important for two major reasons. First, the effects at these sites are detrimental to the performance of normal activities; second, peripheral sensory irritant effects in skin are usually produced only at concentrations several times those required to induce marked peripheral sensory irritation in the eye and respiratory tract.

Eye

Contamination of the eye with a peripheral sensory irritant material causes local pain or discomfort, together with excess lachrymation and blepharospasm as local reflexes, and bradycardia with increased blood pressure as systemic autonomic reflexes. The local discomfort and reflex effects will clearly result in a temporary disturbance of vision. A marked increase in blood pressure, both systolic and diastolic, with moderate bradycardia usually accompanies severe sensory irritation. The cardiovascular effects reverse following cessation of the peripheral sensory irritant stimulus. A typical example is shown in Figure 2.

A further consequence of peripheral sensory irritation of the eye may be a transient moderate increase in intraocular tension. This is most likely to occur following splash contamination of the eye with a liquid sensory irritant (Ballantyne, 1983; Ballantyne et al., 1977a), but has been demonstrated following exposure to vapors (Ballantyne et al., 1976). The cause for the increased intraocular tension produced by peripheral sensory irritant materials is unknown in most instances, but there does appear to be a relationship between the magnitude and duration of increased intraocular tension and the inflammatory potential of the material. This suggests that interference with the local blood flow may be a causal factor in this effect. However, following contamination of one eye with a peripheral sensory irritant, there occurs a rise in intraocular tension both in the contaminated eye and, to a lesser degree, in the contralateral eye (Figure 2). This finding indicates the existence of both local and systemic causes for the increase in intraocular tension (Ballantyne et al., 1977a). Thus, in addition to local changes in blood flow, a variety of other factors of varying importance may be responsible for the induced ocular hypertension; these include squeezing of the eyeballs due to blepharospasm, reflex contraction of the extraocular muscles, and elevation of central venous pressure (Ballantyne et al., 1977a; Collins et al., 1967; Miller, 1967, Rengstorff, 1975). It has been observed that some substances causing transient increases in intraocular tension are not likely to cause marked inflammation, but those producing sustained and marked elevations in tension are frequently injurious to the eye (Ballantyne, 1983; Ballantyne et al., 1973a, 1975, 1977a). The transient increase in tension which occurs with a non-injurious concentration of peripheral sensory irritant material is unlikely to be detrimental to vision, except possibly for a few susceptible individuals in whom there may be precipitation or exacerbation of glaucoma (Ballantyne et al., 1973; Rengstorff, 1975).

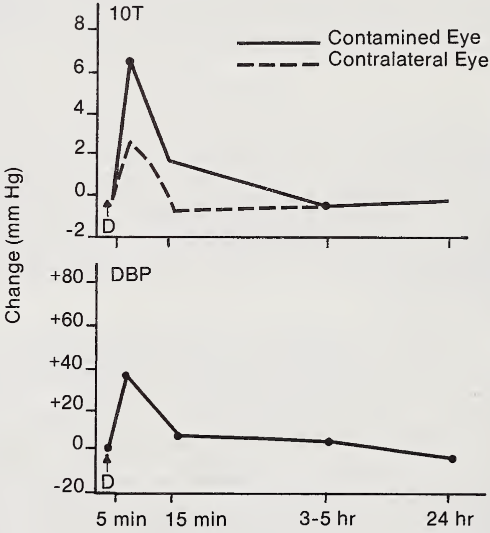

Figure 2: Effects on intraocular pressure (upper graph) and diastolic blood pressure (lower graph) produced by contaminating one eye of a human volunteer subject with an 0.05% (w/v) solution of dibenz(b,f)-1:4-oxazepine in polyethylene glycol 300. There are transient rises of intraocular pressure in both the contaminated and, to a lesser degree, the contralateral eye. There is also a briefly sustained moderate increase in diastolic blood pressure.

Respiratory system

The overall response of the respiratory tract to stimulation by peripheral sensory irritants is more complex than that of the eye. Persons may present with pain or discomfort in the nose, nasopharynx and throat; local reflexes include coughing, sneezing, increased secretions (including rhinorrhoea), increase or decrease in breathing rate, and decreased tidal volume. As with sensory irritation of the eye, there may be transient hypertension with bradycardia. The clinical presentation varies somewhat depending on the nature of the irritant material, and the principal site of receptor activation (Table 1). Stimulation of afferent cholinergic trigeminal fibers in the nasal mucosa leads to a reduction in both the rate of breathing and tidal volume; this is a feature characteristic of materials producing a peripheral sensory irritant response (Cauna et al., 1969; James and Daly, 1969; Ulrich et al., 1972).

A variety of sensory receptors are present in the lower respiratory tract, and their morphology and probable physiological function have been reviewed in detail elsewhere (Grafton and Douglas, 1981; Widdicombe, 1981). With respect to sensitivity to inhaled irritant materials, the most important appear to be the J-receptors and airways irritant receptors. Stimulation of the J-receptor produces apnea, rapid shallow breathing and systemic hypertension with bradycardia. Stimulation of the airways irritant receptor causes hyperpnoea and bronchoconstriction (Douglas, 1981).

TABLE 1: Effects Produced by Stimulation of Respiratory Tract Sensory from Irritant Receptors

Site of Stimulation	Effect	Material
Nasal Mucosa	Decreased breathing rate	Peripheral sensory irritant
	Decreased tidal volume	
Lung	Increased breathing rate*	Inflammatory agents
	Decreased tidal volume	Antigens in sensitized animals
	Bronchospasm	

*A few species have decreased breathing rate (eg. mouse)

The overall effect of stimulation of the lower respiratory tract receptors is, in most species, an increase in breathing rate and tidal volume. This is a characteristic response to peripheral sensory irritant materials which are also capable of causing primary irritation or an allergic response in animals sensitized to the antigen. With many materials, peripheral sensory irritant effects are produced by trigeminal nerve stimulation at concentrations significantly lower than those causing features characteristic of lower respiratory tract receptor stimulation. Therefore, if there is a biologically effective respiratory challenge with a peripheral sensory irritant material, the trigeminal reflex will usually predominate. This difference in sensitivity of response forms the basis for techniques, discussed below, concerned with assessing the margin of warning for respiratory tract injury provided by the peripheral sensory irritant response.

Practical significance of sensory irritation

The biological and practical relevance of peripheral sensory irritant responses may be conveniently considered as follows:

Biological warning

The local sensations produced in response to peripheral sensory irritant materials give a warning of the presence of such materials in the immediate environment. Such biological warning effects will cause affected individuals to seek a source of uncontaminated air. Since peripheral sensory irritant materials may also cause local tissue injury at higher concentrations, a determination of the exposure conditions leading to sensory irritation may be an important factor in determining, or qualifying, exposure guidelines.

Biological protection

The local reflexes resulting from peripheral sensory irritation are of importance as protective mechanisms limiting further exposure. For example, lachrymation removes material from the surface of the eye, and blepharospasm restricts further access of material. With the respiratory tract, decreased breathing rate, decreased tidal volume and cough, all limit inhalation of irritant material.

Harassment and incapacitation

In the context of an occupational environment, both the sensory and the reflex effects may be distracting and harassing, and thus produce variable degrees of incapacitation. For example, intermittent blepharospasm with excess lachrymation produces an impairment of vision and harassment, which is detrimental to efficient working. More important is the fact that the affected individual is likely to be at an increased risk from accidents and physical injury. Peripheral sensory effects may, therefore, be an important cause of impairment of safe and efficient working conditions.

Injury without warning

Whilst the biological importance of a positive peripheral sensory irritant response is clear, the absence of such a response with materials capable of causing tissue injury is also important to know. Such an absence of warning on contact is clearly conducive to injury. Examples of substances which may injure the eye without giving a sensory warning include methyl bromide and dimethyl sulphate (Grant, 1974). In some circumstances, a potent peripheral sensory irritant material has been used as an additive to give warning of the presence of a dangerous material devoid of sensory irritant effects; for example, the former use of chloropicrin in methyl bromide used for fumigation.

In relation to hazard evaluation, recent studies have indicated that certain potent peripheral sensory irritant materials can partially inhibit the phagocytic capacity of pulmonary macrophages (Hogg et al., 1983).

The above considerations clearly indicate that the following are of practical significance in assigning exposure guidelines with respect to peripheral sensory irritation:

i. Peripheral sensory irritation may be a sensitive and early indication of exposure to potentially injurious materials.

ii. Peripheral sensory irritation, particularly when marked, can produce harassing and distracting effects.

It follows that when peripheral sensory irritation is used as a factor in the development of exposure guidelines, there should be reliable concentration-response data. Ideally, such information should include a determination of minimum and no-effects concentrations in order to confidently assign a permissible exposure concentration which will protect the majority of a workforce from the sensory irritant effects of the specific material under consideration.

Quantitative aspects of the sensory irritant response

In keeping with many toxicological phenomena, there is a positive relationship between the proportion of a population responding to a peripheral sensory irritant stimulus and the concentration of the material to which the population is exposed. A linear plot of proportionate response against exposure concentration yields a sigmoid curve typical of many biological responses (Figure 3). This indicates that whilst there is a response by a major proportion of the population over a well-defined range around the median, a small proportion of the population (represented at the left-hand side of the curve) are hypersensitive to sensory irritant stimulation, and also a small proportion (represented at the right-hand side) are hyposensitive. The concentration-response data is usually shown in linear configuration by log-probit plot. As with other acute phenomena, it is possible to calculate a 50% response level, with 95% confidence limits, in order to allow comparison of the potency of different materials with respect to peripheral sensory irritation under defined conditions. However, and as discussed in detail later, in order to obtain the best possible practical estimate of comparative sensory irritant potency it is necessary to consider a variety of other factors, including the slope of the concentration-response regression line.

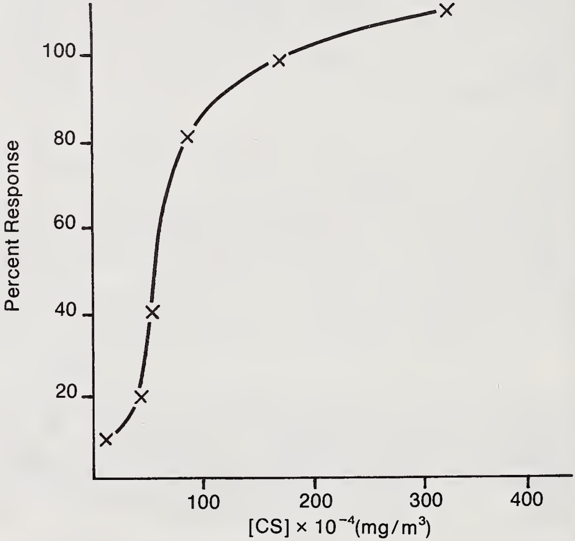

Figure 3: Concentration-response curve for the threshold irritant response to sensation induced by an aerosol of 2-chlorobenzylidene malononitrile (CS) to the human eye. The percent response is the proportion of the population responding for each concentration tested. By probit analysis of the concentration-response data, the TC_{50} (with 95% confidence limits) is 4.0 (2.3-6.6) x 10^{-3} mg/m^3.

A variety of terms, discussed below, are used to numerically express the peripheral sensory irritant response.

For effects that can be objectively evaluated it is common to refer to the effective concentration; ie. a concentration which produces the specific effect under consideration. In such circumstances, and when adequate concentration-response data exist, it is usual to express sensory irritancy potency as the EC_{50}; ie., the concentration, calculated from the concentration-response data, which cause the development of a sensory irritant response in 50% of the population under the specific conditions of the observations. Examples of effects which involve the determination of an effective concentration include blepharospasm and change in breathing rate.

For subjective evaluation, such as the degree of discomfort produced by a sensory irritant, it may be possible to determine a threshold for the induction of discomfort; ie. where the effects are absent or so slight as to pass unnoted. This is clearly of value in defining the concentration region where it is anticipated that peripheral sensory effects will start to appear. In such circumstances, the threshold for a 50% response under the conditions of the observations can be calculated; ie. the TC_{50}. Where information exists on subjective irritation which is suprathreshold, then a further aspect of subjective sensory irritation may be considered; namely, incapacitating effects. These may be defined as effects which are so severe and intolerable as to markedly interfere with the performance of a voluntary activity. In these cases, a concentration causing incapacitation in 50% of the population may be defined; ie. the IC_{50}.

When measurements on specific effects are made in laboratory models for particular peripheral sensory irritant effects, then specific expressions may be used to refer to the effect produced. For example, calculation of the effective concentration to produce 50% depression of breathing rate is usually referred to as the respiratory depression 50, or RD_{50}.

The relationship between exposure concentrations and time to produce defined levels of incapacitation is shown in the left-hand curve of Figure 4. By comparing the three curves for IC_{16}, IC_{50} and IC_{84}, it can be seen that for any given exposure concentration the proportion of the population responding increases with time. This indicates a variable latency between individuals for the same concentration of peripheral sensory irritant material. Also, the curves show that, within certain limits, any given degree of incapacitation or harassment (as expressed in this case of IC_{16}, IC_{50} and IC_{84}) can be produced by a variety of reciprocally related exposure times and concentrations. The reciprocal relationship between time and concentration also has implications for exposure dosage. Figure 4 (right curves) shows that for any given level of incapacitation (ie. fixed proportion of the population responding) exposure dosages are greater for the high concentration-short duration conditions than for the low concentration-long duration exposures. Thus, increasing the exposure concentration shortens the effective response time, but results in a greater exposure dose to produce an equipotent harassing effect.

Factors influencing the peripheral sensory irritant response

A variety of factors, both endogenous and environmental, may influence the concentration required to induce sensory irritation and the latency and duration of effects. Some of the more important of these are briefly discussed below.

Concentration of irritant

The concentration of peripheral sensory irritant is a determinant of the following:

i. The proportion of the population responding, as discussed above and shown in Figure 3.

ii. The latency to onset of effects; in general, the higher the concentration the shorter the time to onset of effects (Figures 4 and 5).

iii. For a brief (pulsed) exposure, the duration of the sensory irritant effect; in general, the higher the concentration the longer the duration (Figure 5).

iv. The higher the concentration the more marked the effect. For example, with increasing concentration an intermittent blepharospasm will become sustained, and threshold sensation becomes progressively more severe until incapacitating pain may be experienced.

Particle size

For peripheral sensory irritants in particulate form, size is an important determinant of both the site and severity of irritant effects. For example, small particles of a respirable size rapidly produce ocular and respiratory effects, whereas large particles produce predominantly ocular irritation with prolonged recovery times. Such a differential effect has been shown, for example, by Owens and Punte (1963) for particles of approximately 1 and 60 µm, MMAD. Findings such as these relate to the membrane fluids, and the influence of particle size on respiratory tract penetration (Ballantyne, 1981).

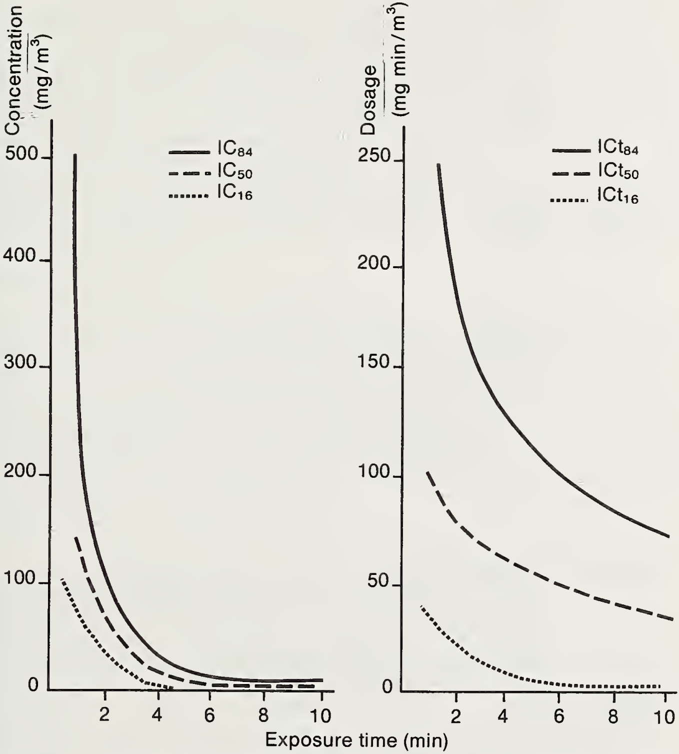

Figure 4: Graphs showing the relationship between concentration and time (left) and exposure dosage and time (right) for defined levels of harassment by chloroacetophenone. The incapacitating concentration (IC) or incapacitating dose (ICt) are plotted as a function of the time required to produce intolerable effects in 16, 50 and 84% of the population studied (Data after McNamara et al., 1968).

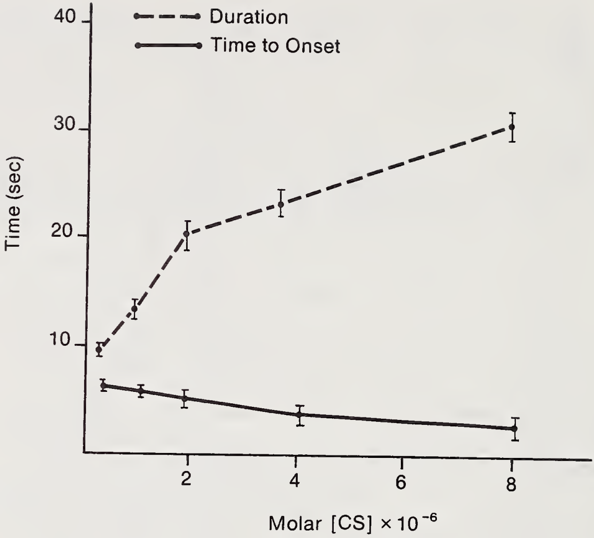

Figure 5: Influence of the concentration of peripheral sensory irritant material, 2-chlorobenzylidene malononitrile (CS), on the latency to onset and duration of eye discomfort. As the concentration of CS increases, there is a decreases in latency and prolongation of duration. Data from Ballantyne and Swanston (1973).

Personality

It is well appreciated that there are significant personality factors in tolerance to pain, and a similar variability exists between individuals with respect to the discomfort produced by peripheral sensory irritants. Under a given set of conditions, some will tolerate the discomfort more readily than others. This is clearly a practical factor when considering the variability of response to sensory irritation in an occupational environment.

Motivation and distraction

Increased motivation and distracting influences generally raise the threshold for induction of peripheral sensory irritant effects, and enhance tolerability for suprathreshold levels of sensory irritancy. Thus, in an occupational environment the concentration at which sensory discomfort is appreciated may be significantly higher than that causing threshold effects in humans under carefully controlled laboratory situations. It follows that the values derived for peripheral sensory irritant materials in experimental situations probably represent the most sensitive index for the effect, and thus represent the most reliable estimates on which to base occupational exposure guidelines.

Tolerance

It is well known that individuals may develop tolerance if exposure to a peripheral sensory irritant is gradual and to low concentrations; ie. the individual adapts by a decrease in the apparent feeling of discomfort and harassment (Beswick et al., 1972). The phenomenon of tolerance is clearly of importance in the workplace, since an adaptation to a warning of potentially harmful chemicals may result in a decrease of safe working conditions. This is a factor which needs to be kept in mind when deciding an appropriate safety margin in assigning workplace exposure guidelines based on peripheral sensory irritation.

Temperature and humidity

It has been determined that environmental temperature and humidity may decrease endurance to peripheral sensory irritation (Punte et al., 1963).

Vehicle

When sensory irritants in solution make contact with body surfaces, then any vehicle used to dissolve the active material may modify sensory irritant potential. Surface active materials, for example, may facilitate penetration and thus enhance irritation as shown by a lowering of the concentration necessary to induce both threshold and incapacitating effects.

Methods for determining peripheral sensory irritant potential

Chemical models

Although some correlations have been made between sensory irritant potential and certain physicochemical characteristics, this has only been for a few and limited series of materials. Information is sparse on the influence of differing chemical classes on sensory irritancy, and on comparisons between the physicochemical properties of irritant versus non-irritant species. However, experimental studies indicate that sensory irritants may become membrane bound at particular affinity sites (Green et al., 1979).

In an attempt to predict materials likely to be peripheral sensory irritants, a variety of artificial membranes have been used to stimulate reactivity with biological membranes. These have included monolayers and bilayers of lecithin, with monitoring of phase transitions to measure interaction. Techniques used to investigate transitions include differential scanning calorimetry, electron spin resonance and X-ray diffraction. The use of these artificial membranes has not generally been promising as a reliable screening method for sensory irritant potential.

Biological models

A variety of biological models, of varying degrees of sophistication, are available for assessing the qualitative and quantitative potential of substances to cause peripheral sensory irritation. Some of the more commonly used are briefly reviewed below.

Isolated intestinal segment

This is a nonspecific method based on the use of isolated segments of intestine which are suspended in an incubating bath and supported to allow contraction of the segment to be mechanically detected. Sensory irritant is added to the bath at varying concentrations and a determination made of those concentrations causing contraction of the segment.

Frog flexor reflex

This also is a general and nonspecific method, which involves a determination of the minimum concentration of irritant required to cause withdrawal of the hind-limb of decerebrate frogs from test solutions. This approach has found use as a reliable screening test for materials having peripheral sensory irritant potential (Feniak, 1966).

Blepharospasm test

The induction of blepharospasm in conscious animals in response to topically applied solutions or to materials dispersed in the atmosphere is a technique frequently used to assess the potential of a substance to cause sensory irritant effects on the eye. It is a simple and reliable method for this purpose. For solutions, the test involves applying increasing concentrations of the substance to the surface of the cornea, and recording the proportion of the population which develops blepharospasm following the initial blink reflex. In this way a

As discussed previously, for any given substance there is usually a marked difference in the concentration causing a typical sensory irritant response by stimulation of sensory receptors in the nasal mucosa and that concentration necessary to stimulate pulmonary receptors. In most instances, in the intact conscious animal, the nasal trigeminal response will dominate. It follows that determination of the difference between these concentrations may be used as an index of the margin of warning for potential injury provided by the peripheral sensory irritant response. A considerable amount of valuable work has been conducted in this area by Alarie and his co-workers who use intact mice to determine the peripheral sensory irritant response from trigeminal nerve stimulation, and tracheal cannulated mice to measure the pulmonary receptor response (Alarie, 1981a). The mouse, unlike other species, undergoes a decrease in breathing rate in response to pulmonary receptor stimulation. The expression $[RD_{50}(TC)/RD_{50}]$, which is the ratio of the concentration causing decrease in breathing in cannulated mice versus that in intact mice, may be used as a guide to the margin of safety produced by sensory irritant warning, but with hydrogen chloride the concentration likely to cause lung injury is close to that giving a sensory irritant warning. Rapid objective methods are being developed to measure lung injury and allow comparison with sensory irritant effects. These include measurement of changes in respiratory function, including resistance (Matijak-Schaper et al., 1983) and detection of pulmonary edema by a sensitive method based on injection of ^{51}Cr-ethylenediamine tetra-acetic acid followed by lung lavage (Valentini et al., 1983).

Studies in human subjects

The various animal studies discussed above allow the detection of materials causing peripheral sensory irritant effects based on the reflex changes induced. They do not, however, allow for the assessment of subjective discomfort or pain, which is an important component for the evaluation of peripheral sensory irritation in humans. In view of this, and because of the difference in sensitivity between animal models and humans to certain peripheral sensory irritant materials, it is desirable to conduct tests for assessing irritant potential in human volunteer subjects. Such tests should, of course, only be conducted providing that there is adequate information on the toxicology of the material to ensure that the procedure carries no risk for the volunteers. Such studies allow not only a quantitative assessment of sensory irritant potential at threshold and suprathreshold levels, but allow a determination of variability and the influence of environment factors on the response.

Eye irritation

As with the animal models, it is possible to determine the concentration of irritant which causes blepharospasm in human subjects. In addition, however, it is also possible to determine the degree of local discomfort produced at various concentrations, and define a threshold for sensation and an indication of concentrations causing marked discomfort. Peripheral sensory irritation of the eye may be relatively easily assessed for solutions by the direct application of carefully measured droplets (Ballantyne et al., 1973, 1974). For vapors or gases, tests may be conducted in a chamber with the subject wearing respiratory protective equipment, or using a chamber specially equipped with eye ports (Bender et al., 1983). Table 2 shows some examples of EC_{50} for blepharospasm and TC_{50} for sensation in humans. These examples demonstrate that the human eye is more sensitive to blepharospasm-inducing effect of the materials tested than either the rabbit or guinea pig eye. Also, with humans the most sensitive indication of a peripheral sensory irritant effect on the eye is sensory discomfort.

TABLE 2: Comparison of the Quantitative Response to Two Peripheral Sensory Irritant Materials, 2-Chlorobenzylidene Malononitrile (CS) and Dibenz(b,f)-1:4-Oxazepine (CR): Solutions in Polyethylene Glycol 300 applied to the eye*

Material	Blepharospasm EC_{50} (molar)**			Sensation TC_{50} (molar)**
	Guinea Pig	Rabbit	Man	Man
CS	2.2 (1.9–2.4) x 10^{-5}	5.9 (3.8–10.0) x 10^{-5}	3.2 (2.1–6.1) x 10^{-6}	7.3 (4.2–11.2) x 10^{-7}
CR	3.5 (2.8–4.3) x 10^{-5}	7.9 (5.1–12.5) x 10^{-5}	8.6 (6.8–12.5) x 10^{-7}	4.9 (3.8–6.5) x 10^{-7}

* Data after Ballantyne and Swanston (1973, 1974)

** Expressed as 50% response with 95% confidence limits

Inhalation

For respiratory tract irritation it is usual to determine the concentration causing discomfort; for example, chest pain, cough or nasal irritation. Exposures may be conducted in chambers of a size sufficient to comfortably house the volunteers, and equipped with facilities for sampling the atmosphere in the breathing zone. In some instances a wind tunnel may offer a convenient exposure environment to control and alter concentrations of the test material. In order to avoid complications due to ocular stimulation, either comfortable airtight goggles may be worn or the irritant delivered by mask.

Skin

To determine the degree of discomfort produced by applying a peripheral sensory irritant material to the skin, various concentrations of the substance can be used and the discomfort produced subjectively assessed. In choosing the site, it is important to remember that there are anatomical regional variations in the sensitivity of skin to peripheral sensory irritation (Ballantyne et al., 1973b).

Since the epidermis presents a barrier for the access of peripheral sensory irritant substances to subepidermal sensory nerve receptors, a method which has been used to overcome this and obtain a comparative evaluation of substances is the blister base technique. This involves the creation of a blister on the forearm by covering the area with a tape having perforations at regular intervals, to which is applied a paste of 0.2% cantharidin in kaolin. The tape and paste are removed after six hours and the blisters allowed to develop overnight.

Interpretation and application of information on peripheral sensory irritation

Ideally, information derived from the use of animal models should give an indication of the concentration range over which sensory irritant effects may be expected to occur in humans. However, most animal models are less sensitive to peripheral sensory irritants than is the human, particularly to the subjective effects. In general, studies with animal models can detect those materials having a potential to produce peripheral sensory irritant effects, but they generally do not rank different substances in their order of potency for humans. Also, they usually cannot accurately predict the concentration range over which effects may be anticipated in humans.

An example of the difference in the assessment of the relative potency of materials is provided by a comparison of three potent peripheral sensory irritant materials; 2-chlorobenzylidene malononitrile (CS), dibenz(b,f)-1:4-oxazepine

(CR) and chloroacetophenone (CN). By determination of mouse RD_{50} (Figure 6), TC_{50} for blepharospasm in rodents (Table 2), and frog flexor reflex (Feniak, 1966), CS is a more potent sensory irritant than CR. However, studies on humans demonstrate a relatively greater potency for CR than for CS by exposure of the eye, tongue and respiratory tract (Ballantyne, 1977; Ballantyne and Swanston, 1973, 1974). In contrast, the relative potency by mouse RD_{50} of 5:1 for CS/CN (Figure 6) accords with the 10:1 (CS/CN potency reported for humans (Himsworth Report, 1971). Although experimental animal studies are generally not applicable to a quantitative evaluation for humans, some methods for peripheral sensory irritation have been used as a basis for predicting acceptable levels of exposure for the workplace. For example, Alarie (1981b) has shown a good correlation between Time Weighted Average Threshold Limit Values (American Conference of Governmental Industrial Hygienists, 1983) based on irritancy and the numerical value of 0.03 RD_{50} as determined in mice.

In comparing the relative potency of different sensory irritant materials, and when adequate concentration-response data are available, it is important to review the EC_{50} and 95% confidence limits to determine if there are significant differences in potency at the 50% response level. However, and as with any analysis of dose-response information, it is of the utmost importance to take into consideration the slope of the regression line. For example, if two materials have significantly different EC_{50} values and the slopes of the dose-response regression lines are essentially parallel, then it can be confidently stated that the two materials are significantly different over a wide range of concentrations with respect to peripheral sensory irritant potency under the conditions of the study (Figure 7). In contrast, if the slopes are not similar this may have important influences on the differential interpretation of the practical relevance of the data. For example, the two materials shown in Figure 7 have identical EC_{50} values and 95% confidence limits, indicating no difference in peripheral sensory irritant potency at the 50% response level. However, because of differences in the slopes of the regression lines there are significant differences between the two materials for sensory irritant potency at the high response (EC_{95}) and low response (EC_5) regions; this has important implications on the interpretation of these data. For the material having the steeper slope, once a concentration is reached which causes sensory irritation in a minor proportion of the exposed population, then only a small incremental increase is necessary to cause an effect in the majority of the population. Thus, in such circumstances it may be necessary to add a wide margin below this restricted concentration range in order to ensure adequate protection. In contrast, with the material having a shallow slope, the concentration range over which the majority of the population will be affected is much greater. However, and because of the shallow slope there will

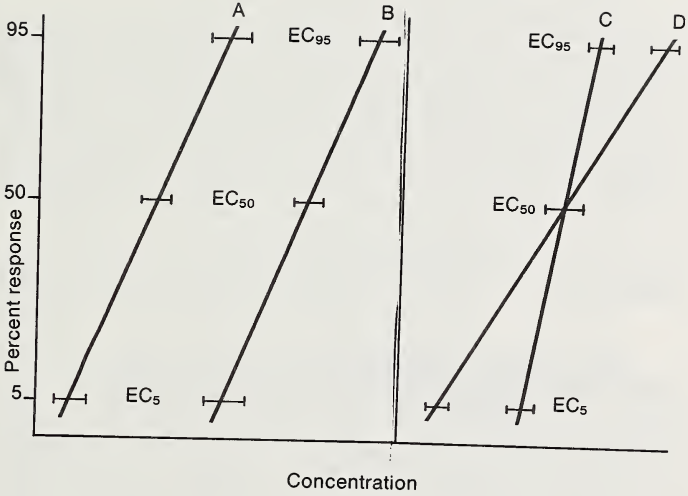

Figure 7: Schematic representation for the comparison of the sensory irritant potency of materials. The two substances A and B (left-hand graph) have similar slopes and do not have overlapping 95% confidence limits (as shown by the horizontal bars). They may be considered to be statistically significantly different with respect to peripheral sensory irritant potential over a wide range of concentration, with material A being more potent than that for B. With materials C and D, however, although they have statistically significantly identical EC_{50} values, the slopes of the regression lines are different and therefore the EC_5 are also different. This implies a concern for hypersensitive individuals with material D, and a narrow range of concentration over which the majority of the population will respond with material C.

clearly be an interest in protecting the small proportion of the population who are hypersensitive. Assuming tissue injuring effects occur at concentrations above those causing sensory irritation, then an exposure guideline based on hypersensitivity to peripheral sensory irritation should offer excellent protection to the remainder of the workforce.

It follows from the above discussion that when the sensory irritant potential of different substances are being compared it is necessary to consider both the 50% response level (with 95% confidence limits) and the slope of the concentration-response regression line. The fact that slopes may differ from various substances has two implications. First, it may not be possible to calculate a true statistical potency ratio. Second, the relative potency of two materials can vary for differing levels of sensory irritation. Although it may not be possible to calculate a potency ratio, it can be useful to determine the comparative potency of materials at different levels of irritancy (Ballantyne, 1977); this may be defined as follows:

$$\text{Comparative Potency (A-B)} = \frac{\text{Concentration of A causing a defined response}}{\text{Concentration of B causing the same response}}$$

Also, during considerations of the relevance of incapacitating effects of peripheral sensory irritation it is useful to compare the threshold levels (TC_{50}) and incapacitating levels (IC_{50}) in order to determine if the difference between these values is sufficient to enable threshold effects to give sufficient warning of a potentially incapacitating exposure. A useful expression is the ratio IC_{50}/TC_{50}; the "effectiveness ratio". A high value for the effectiveness ratio indicates that threshold irritation will give a good warning of potentially incapacitating effects. However, if the ratio is small, then a small incremental increase in concentration will convert a threshold effect into an incapacitating effect. Clearly this will influence the decision on the need for an additional margin for the exposure guideline over that applicable to materials having a high effectiveness ratio. For example, using the data shown in Table 3, the IC_{50}/TC_{50} for CS and CR are respectively, 900 and 350. This indicates that although there is a significant margin between the threshold and incapacitating concentrations for both materials, the proportionate increase in atmospheric concentrations to convert a threshold effect to an incapacitating effect does not have to be as great with CR as with CS. Another feature of importance in comparing threshold and incapacitating effects is shown in Table 3; namely, that the comparative potency of two materials may differ at the threshold level from that at the incapacitating level, because of differences in their concentration-response lines. For example, the comparative potency data at the TC_{50} level indicates CR to be twice as potent as CS, but at the IC_{50} and IC_{75} levels of incapacitation CR is 5 and 9 times, respectively, more potent than CS.

When assessing the relevance of information derived for a particular material, data on the threshold concentration for induction of peripheral sensory irritant effects is clearly desirable as a starting point. However, decisions on what margins of safety may be required to be adopted over threshold concentrations will be influenced by factors such as the increase in concentration necessary to convert a threshold into an incapacitating effect. Also, consideration on the adequacy, or otherwise, of the warning provided by peripheral sensory irritant effects will clearly influence the relative importance of peripheral sensory irritation in assigning workplace exposure guidelines.

Although, in a few cases, peripheral sensory irritant effects may be the major determinant of exposure guidelines, in most cases it is necessary to compare potency for sensory irritancy with that for definitive toxicity or tissue injury. This may be approached as follows:

TABLE 3: Comparison of the Potency of Aerosols of Two Peripheral Sensory Irritant Materials at Differing Levels of Effect; 2-Chloro-Benzylidene Malononitrile (CS) and Dibenz(b,f)-1:4-Oxazepine (CR)*

Material	Level of Irritancy (mg/m^3)**			Effectiveness Ratio	
	TC_{50}	IC_{50}	IC_{75}	IC_{50}/TC_{50}	IC_{50}/TC_{50}
CS	4.0×10^{-3}	3.6	10.0	900	2500
CR	2.0×10^{-3}	0.7	1.1	350	550
Comparative Potency (CS/CR)		2.0	5.1	9.1	

* Data from Ballantyne (1977).

** Slopes of the regression lines for incapacitation: 1.5 for CS, 2.9 for CR.

i. Quantitative comparison of the concentrations (or dosages) necessary to produce sensory irritation and toxic effects at a given target tissue or organ. This would include, for example, estimation of the $[RD_{50}(TC)/RD_{50}]$ by inhalation; or determination of the threshold for peripheral sensory irritation of the eye and the threshold to produce corneal injury or conjunctivitis.

ii. Determination of the threshold to produce peripheral sensory irritation at the most sensitive target tissue, and comparison with the concentration known to produce threshold local injury or systemic toxicity as derived from other sources of information, including observations on exposed human populations.

Peripheral sensory irritation may be considered in discussions on exposure guidelines under the following circumstances:

a) When the available evidence indicates that the irritant effect is the most significant biological effect, because of its potential to cause incapacitation at concentrations significantly less than those causing other forms of toxicity. In this circumstance it is essential to have information on the threshold to produce effects in order to assign the most appropriate guideline. The exposure guideline so derived will protect for the abrupt and possibly incapacitating effects of peripheral sensory irritation, the reflex cardiovascular consequences of acute peripheral sensory irritation, and any local or systemic toxicity. In this case where peripheral sensory irritation offers an excellent or acceptable margin of warning of the potential for tissue injury, it will be necessary only to allow for an incremental decrease below the threshold for sensory irritancy in order to ensure protection.

b) When sensory irritancy is not the most significant biological effect, but where it may be a sufficiently sensitive index for adverse health effects produced at higher concentrations. In such cases, the data on sensory irritation can be used as a qualification for exposure conditions. Also, the concentration difference between that causing threshold sensory irritation and that which is regarded as giving an adequate degree of protection, may be significantly greater than is the case with (a). The exposure guidelines will be determined in such cases mainly by the nature of the tissue injury produced.

c) Where toxic effects are produced at concentrations below those causing sensory irritation. In such circumstances sensory irritation can only be used as an indication of over-exposure situations. Workplace exposure guidelines will be set entirely on consideration of the nature of the tissue injury produced.

d) Some materials capable of producing serious adverse health effects may not give any sensory irritant warning on contact. Any discomfort produced is a direct consequence of tissue injury. It is important to be aware of these materials because of the potentially insidious nature of their tissue injuring effect, and the fact that warning of toxicologically significant over-exposure will not occur.

In general, the various quantitatively defined workplace exposure guidelines are derived as follows: The 8-hour time-weighted average exposure guideline is often based on consideration of systemic toxicity by repeated exposure. The short-term exposure limit, which is a 15-minute time-weighted average that should not be repeated more than four times per day with an interval of at least one hour between successive exposures at this level, is generally applied in circumstances where short-term exposure to high concentrations may result in acute toxic effects. It is, therefore, a value which is often used to qualify the 8-hour time-weighted average for a substance whose toxic effect primarily results from chronic exposure conditions, but which also has recognized acute toxic effects. The 'ceiling' is a concentration limit that should not be exceeded even instantaneously, and therefore is applicable to those substances producing effects which are rapid in onset and liable to produce immediate tissue injury or create a situation which compromises the safety of the individual. It follows that the 'ceiling' concept is usually the most appropriate for controlling peripheral sensory irritant materials in the workplace.

Peripheral sensory irritation finds its main use as a factor in defining exposure guidelines where (a) irritation is a prime consideration due to its potency, and (b) the warning potential of irritation can be used as a qualifier for those materials likely to induce adverse health effects by acute short-term repeated exposure and, to a lesser extent, where chronic exposure produces non-genotoxic injury. In these circumstances there is reasonable evidence for the existence of a threshold for tissue injury. Sensory irritation may qualify the upper level of excursion on exposures if it occurs at concentrations below the threshold for toxicity. In contrast with those materials causing, or suspect of causing, oncogenic, mutagenic, or adverse reproductive effects, where the concept of a threshold is debatable, peripheral sensory irritation will generally be a minor consideration.

Summary

Peripheral sensory irritant materials interact with sensory receptors in body surface membranes, causing local discomfort and reflexes which are both systemic and local in type.

Biologically the effects are warning and protective, but in the workplace may cause a situation which is detrimental to safe and efficient working. For occupational exposure considerations, the principal sites of interest are the eye and respiratory tract. Chemical models are not currently promising for the prediction of materials with sensory irritant potential, but a variety of animal models are available which will detect sensory irritant substances. With human volunteer subjects it is possible to quantitatively define threshold and incapacitating levels. Peripheral sensory irritation is a major consideration in assigning exposure guidelines to materials where this is the primary effect, and from which protection is necessary to prevent injury which could be a consequence of a harassing effect of sensory irritation. More frequently, peripheral sensory irritation is used to qualify exposure guidelines where irritant effects occur at concentrations of the material lower than those causing tissue injury by acute or repeated exposure. In these circumstances control for sensory irritant effects will provide an adequate margin for protection against toxic effects

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PARTICULATE OIL SHALE INHALATION AND PULMONARY INFLAMMATORY RESPONSE IN RATS

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Abstract

Large scale shale-oil production in the U.S. will raise questions about potential occupational lung injury to workers exposed to products associated with processing oil shale. In this study, several parameters of lung inflammation were measured in rodents exposed to either oil shale dust or quartz (positive control) and in age matched controls. Animals were exposed to aerosols six hours/day, four days/week for 30, 90, 180, 270, and 365 days. They were sacrificed immediately after exposure or after 7 or 30 days recovery. Injury was assessed by histopathology of tissue sections, characterization of cellular and fluid components of lavage samples, and quantitation of collagen. Characterization of lavage samples included: 1) total cell count, 2) cell differential, 3) flow cytometric analysis of cells for DNA content, and 4) presence of elastase in the fluid. Histology revealed minimal differences between the treated groups. Statistical comparisons of the lavage samples and elastase measurements showed indications of predictable but variable inflammatory response by analysis of covariants and multiple range tests. On the basis of the 30-365 day exposures, the animals, and the differences were elucidated by the data from all the assays used.

Pathology on 6 and 12 month quartz-exposed animals showed a localization of quartz at the plueral surface associated with granulamos. Integration of the data from all the assays illustrates the temporal progression of response, the effects of cessation of insult and the potential for permanent latent injury. This work was supported by the U.S. Department of Energy.

Introduction

Oil shale deposits located in the western United States provide an unexploited source of domestic crude oil. Development of this resource has been limited by economics;

however, recent reduction of recovery costs coupled with the possibility of liquid fuel shortages encourage continued development of improved recovery technologies. Along with technology development, a parallel effort to define the potential occupational and environmental hazards associated with extraction of oil from oil shale is ongoing at the Life Sciences Division of the Los Alamos National Laboratory. The present status of this industry and the prospect that it could expand to full capacity present a singular opportunity to define hazards which will facilitate industrial hygiene and environmental controls as part of the development, growth and expansion of the industry. This study presents one facet of our efforts to define the hazards and to understand the mechanisms that may result from inhalation of the several dusts inherent in the processing of oil shale.

In this study we investigate: 1) the progression of biological response following shale- and quartz-dust inhalation; 2) recovery following cessation of exposure and 3) the potential for permanent injury. Two endpoints were of primary importance: fibrosis and tumorigenesis, which can occur separately or in parallel. Our study concentrated on the events resulting in pulmonary fibrosis. In addition to collecting data at 1, 3, 6 and 12 months of exposure, we included sufficient animals to harvest samples at several intervals after the exposure ended. Each sacrifice point has three sample elements: 1) those taken immediately after termination of exposure; 2) those taken 7 days after termination of exposure; and 3) those taken 30 days after termination of exposure.

Materials and methods

Female Fischer-344 rats were exposed to well characterized aerosols of raw oil shale or quartz (Minusil, Pittsburgh Sand and Glass Co.). Groups of rats were exposed to the aerosols in a nose-only configuration (1). The exposures were conducted for 6 hours on each of 4 days/week for periods of 1,3,6 and 12 months. The mass concentration of shale dust aerosol was 10 mg/m^3. Equal numbers of animals were exposed as positive controls for fibrogenesis to an aerosol of quartz for the same 1-, 3-, 6-, and 12-month periods. The quartz concentration was established at 1 mg/m^3, because raw oil shale contains about 10% quartz, therefore, exposing all groups to approximately equivalent quartz levels. The quartz aerosol had a mass medium aerodynamic diameter (MMAD) of approximately one micron (S.D. = 1.8). The MMAD for shale dust was approximately two microns (S.D. = 1.8), as determined by cascade impactor sampling. To complete the study a group of age-matched cage controls were maintained in the same animal rooms.

Animals were randomly selected for sacrifice with four animals from each of the two exposure groups and the control group euthanized by intraperitoneal injection of pentabarbitol sodium (25 mg). The lungs were surgically exposed and the left lung isolated by ligating the left bronchus. The lobes of the right lung were lavaged four times with 5 mL of normal saline and subsequently fixed in 10% formalin for histological evaluation. The left lung was frozen for collagen analysis. The collagen assay has been described (2). Briefly, it involves acid hydrolysis and purification of hydroxy-proline, a building block of collagen, followed by colorimetric quantitation. The lavage fluids were separated into fluid and cellular components. The fluid portion was frozen (4°C) and later thawed and assayed for elastase by the Enzyme Labelled Substrate Assay (ELSA) method (3). Total and differential cell counts were determined for the cellular fractions. Microscopic examination of the right lobes was performed on all lungs.

Results

We proposed that presence of increased elastase levels in the lavage fluids could be a measure of evolving lung tissue injury. Decreased elastase levels were observed in the quartz-exposed animals when compared to controls at the 3- and 6-month exposure points (Figure 1). The shale-exposed animals had lavage fluid elastase levels higher than those from the quartz-exposed and comparable to control values at both these points. At 12 months, the shale-treated animals exhibited values significantly higher than controls, while the values of the quartz-exposed animals compared to controls were not significantly different.

Exfoliative cells from the lung have long been used to evaluate responses to inhaled materials in an effort to predict dysfunction or disease (4). Pulmonary alveolar macrophages (PAM) comprise the majority of the cells in lavage fluids. Other constituents are polymorphonuclear cells (PMN), lymphocytes, and epithelial cells. Two important criteria for assessing change or response are total cell yield and the relative numbers of each cell type.

The average cell yield from control animals was about two million cells at each time point over the course of the experiment (Table I). The total cell yield for the shale-treated animals was not significantly different from the age-matched controls at any of the sacrifice dates. For the quartz-exposed animals, the harvests at 6 and 12 months were significantly different, being elevated to 2.7-2.9 million cells ($p<.05$). The volumes retrieved in all cases were comparable, between 16 and 19 mL. The number of PMN steadily increased with time for both shale- and quartz-treated animals with the latter showing the greatest increases. Table I shows the increasing cell yields from quartz-exposed animals, a decreasing number of PAM and increasing numbers of lymphocytes and PMN. Numbers of PAM are not significantly different from controls for either

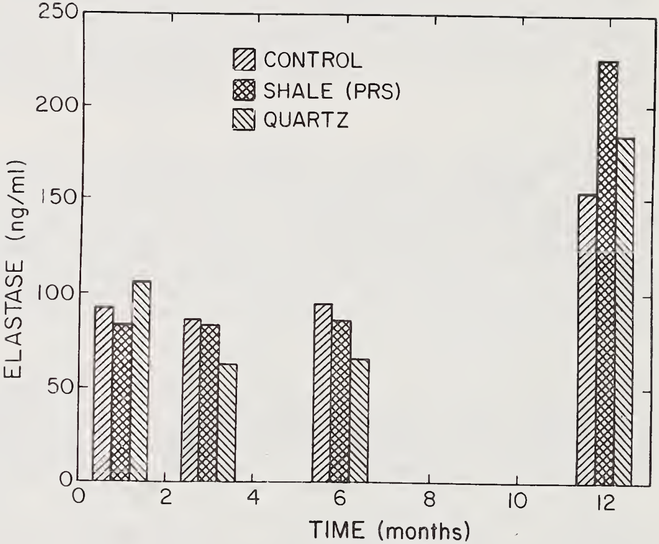

Figure 1: Elastase levels (g/ml) in lavage fluids from quartz-exposed, shale-exposed, and control animals. There were no significantly different values for either of the treated groups compared to the controls, except for the shale-exposed animals at 12 months.

TABLE I: Total cell yields and differentials for treated and control animals after 1-,3-,6-, and 12-month exposures. (Total cell yields increased for the quartz-exposed animals by 6- and 12-months as a result of increases in lymphocytes and PMNs)

Length of exp.	Treatment Group	Total Cell Yield	PAM	Numbers of Lymphs	PMN
(months)		(x 10^6)		(x 10^6)	
1	Control	2.1 ± 0.2	1.7 ± 0.1	0.3 ± 0.1	0
1	Shale	2.7 ± 0.5	2.0 ± 0.1	0.5 ± 0.5	0.04 ± 0.4
1	Quartz	2.2 ± 0.7	1.5 ± 0.1	0.6 ± 0.6	0.02 ± 0.02
3	Control	1.8 ± 0.1	1.6 ± 0.1	0.2 ± 0.02	0
3	Shale	1.7 ± 0.3	1.5 ± 0.3*	0.1 ± 0.05	0
3	Quartz	1.3 ± 0.1	0.9 ± 0.1#	0.3 ± 0.1	0.03 ± 0.03
6	Control	1.5 ± 0.3	1.2 ± 0.2	0.1 ± 0.1	0.01 ± 0.02
6	Shale	1.3 ± 0.5*	1.0 ± 0.4	0.1 ± 0.4	0.16 ± 0.08#
6	Quartz	2.7 ± 0.5#	1.5 ± 0.3	0.4 ± 0.3#	0.67 ± 0.19#
12	Control	1.5 ± 0.5	1.2 ± 0.5	0.1 ± 0.03	0.03 ± 0.01
12	Shale	1.5 ± 0.1*	1.0 ± 0.1	0.2 ± 0.05*	0.20 ± 0.11#
12	Quartz	2.9 ± 1.2#	1.2 ± 0.7	0.7 ± 0.3#	0.83 ± 0.30#

* Value is significantly different from quartz value at 95% confidence level by Student's t test.

# Value is significantly different from control at 95% confidence level by Student's t test.

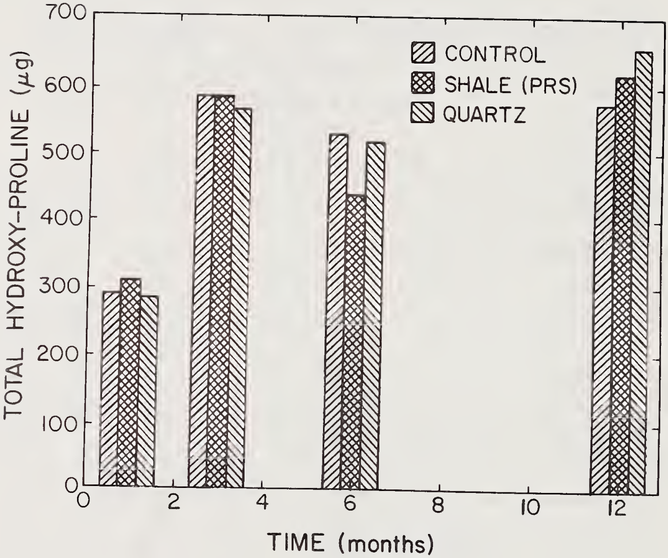

Figure 2: Hydroxyl-proline levels in the left lungs of all exposed and control animals. Comparisons at 1, 3, 6, and 12 months of exposure show no significant differences for either of the treated groups versus the controls.

TABLE II: Total cell yields and differentials for 6- and 12-month exposures following 7 or 30 days of recovery. Persistent increases in numbers of PMN and lymphocytes are evident for the quartz-exposed animals after 6 months, but only at 12 months of exposure for the shale-treated animals

Time*	Treatment Group	Total Cell Yield	PAM	Numbers of Lymphs	PMN
		(x 10^6)		(x 10^6)	
6/7	Control	1.6 ± 0.2	1.4 ± 0.2	0.12 ± 0.03	0.03 ± 0.03
6/7	Shale	1.4 ± 0.3	1.2 ± 0.3	0.10 ± 0.04#	0.07 ± 0.03
6/7	Quartz	2.1 ± 0.6	0.9 ± 0.3@	0.24 ± 0.1@	0.86 ± 0.4@
6/30	Control	2.4 ± 0.5	3.2 ± 0.2	0.23 ± 0.3	0.06 ± 0.2
6/30	Shale	2.2 ± 0.7	1.7 ± 0.6#@	0.10 ± 0.02	0.09 ± 0.02
6/30	Quartz	5.7 ± 1.4@	2.9 ± 0.7	1.17 ± 0.5@	1.47 ± 0.6@
12/7	Control	1.6 ± 0.4	1.3 ± 0.4	0.15 ± 0.03	0.04 ± 0.02
12/7	Shale	2.4 ± 2.0	0.81 ± 0.2	0.15 ± 0.07	0.1 ± 0.07#
12/7	Quartz	3.6 ± 0.8	1.6 ± 0.6	0.67 ± 0.4@	1.11 ± 0.2@
12/30	Control	1.8 ± 0.5	1.4 ± 0.3	0.13 ± 0.10	0.06 ± 0.05
12/30	Shale	3.7 ± 1.4	2.8 ± 1.2@	0.38 ± 0.18#@	0.32 ± 0.13@
12/30	Quartz	5.9 ± 1.3	2.9 ± 0.8@	0.74 ± 0.3@	2.1 ± 0.6@

* Months of Exposure/Days or Recovery

# Value is significantly different from quartz value at 95% confidence level by Student's t test.

@ Value is significantly different from control at 95% confidence level by Student's t test.

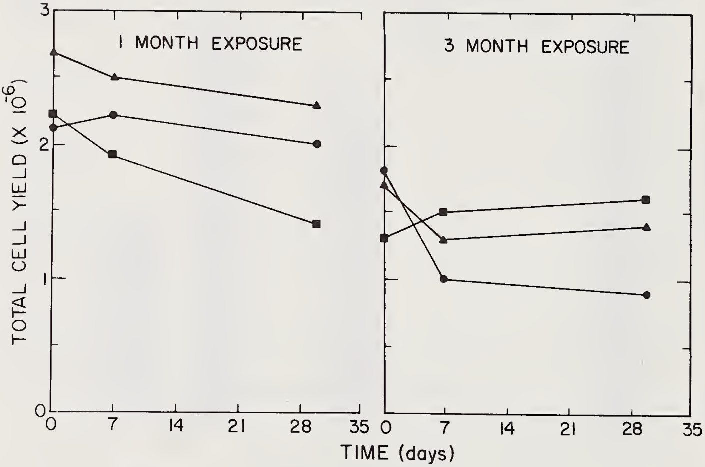

Figure 3: Lavaged cell yields after 1 and 3 months of exposure to quartz (☐) or shale (△) along with age-matched controls (○) show no significant differences. At t=0, treatment is discontinued and subsequent data points are plotted after recovery periods of 7 and 30 days.

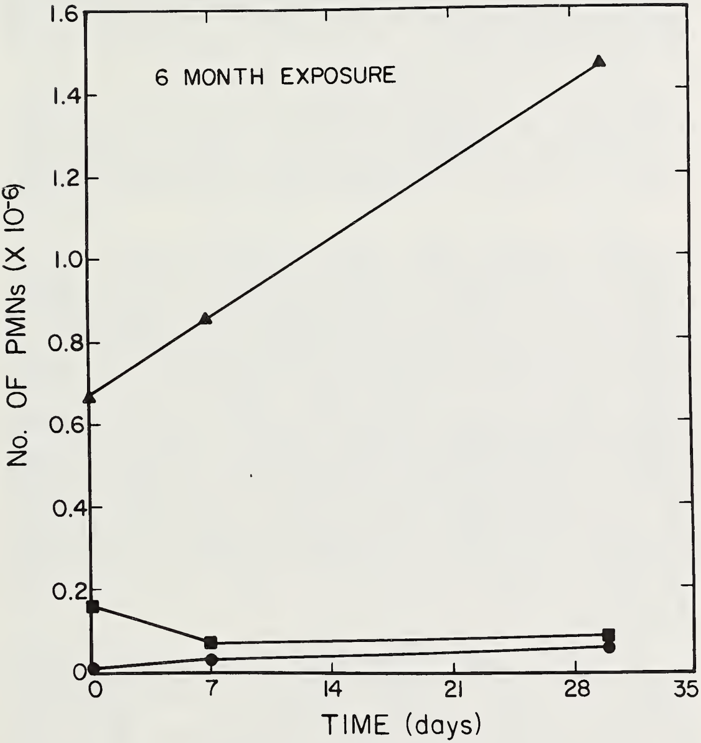

Figure 4: After a 6-month exposure to quartz (□) or shale (△) the number of PMNs harvested from the quartz-exposed, t=0 is elevated. Treatment was discontinued and the number of PMNs harvested after 7 and 30 days recovery continued to rise for the quartz-treated animals. Controls (○) show no changes.

shale- or quartz-exposed animals except for the 3-month exposures, at which time PAM are significantly depressed from shale-exposed and controls. All of these observations are for the samples taken from the animals sacrificed immediately after cessation of exposure.

Levels of hydroxy-proline, a constituent of collagen, showed a small but steady increase over the course of the experiment in all groups, but there were no significant differences between the controls and the treated animals (Figure 2). The last collagen data taken for the 12-month exposures showed a significant increase in the quartz-exposed group compared to controls. Shale-exposed animals exhibited increased levels that were not statistically significant.

When the animals were allowed a recovery period of 7 or 30 days, the changes in PAM and PMN abundance were even more dramatic. Again, at the earliest sacrifices (1 and 3 months) there were no changes in relative numbers of PAM or PMN as reflected in the total cell yields (Figure 3). However, at six months the total cell yields increased almost exclusively as a result of an increase in PMN (Figure 4); macrophage numbers for both shale and quartz-treated samples remained near control levels (Table II). By 12 months of exposure, the total cell yields after 7 days recovery were elevated for both groups compared to controls and were even more so at the 30-day recovery point. These increases are due to elevated numbers of lymphocytes and PMN after 7 days recovery and after 30 days both shale- and quartz-exposed have significant increases in PAM, lymphocytes and PMN. In conjunction with this, no significant lesions were noted microscopically in the shale-exposed animals, but at 6 months several quartz-exposed animals had pneumonia, granulomas or fibrosis, alone or in combination. At 12 months of exposure, all the quartz-exposed animals had developed granulomas, while the shale-exposed animals remained devoid of significant lesions.

Discussion

Our goal in this endeavor was to define the temporal response of the lung to inhaled shale dust and to compare these findings with those in animals exposed to a known fibrogenic agent. During the course of the experiment, lavaged cells indicated inflammatory responses to both shale and quartz, but the responses to quartz were more pronounced. When the animals were allowed a recovery period after treatment, those from the later time points had a greater influx of PMN for both treated groups. The increase in the number of cells harvested resulted almost exclusively from an increase in PMN and lymphocytes.

Both macrophages and PMN contain lysosomal enzymes, including elastase, a neutral protease with specific lytic activity for native soluble collagen and active at neutral pH.

We assayed the lavage fluids for elastase expecting to find increases at some time during the course of data collection. However, there were no significant differences between controls and treated groups. At this time it's unclear whether the lack of any specific change was the result of technique insensitivity or actually reflected biological response. Quantification of collagen present in the left lung failed to indicate any temporal graduations or differences in effects between groups. It is conceivable that 12 months of exposure was the point at which, under the conditions of this experiment, excess collagen would become apparent. Analysis of lungs from animals exposed 18 and 24 months might reveal differences.

Conclusions

In summary, this experiment indicates that long-term inhalation of shale dusts by rats elicits a limited inflammatory response in the lung less profound than that observed in animals exposed to equivalent levels of quartz alone. This observation is significant because, while the concentration of quartz used was equivalent to the amount found in the shale, shale contains organic and inorganic constituents that may provide a protective effect. The implications for fibrogenic disease are two-fold: 1) inhalation of oil shale dusts appeared to be less detrimental than the inhalation of quartz alone, and 2) there was no apparent synergistic action of quartz and the complex of organic materials present in shale. Animals exposed to shale dusts failed to develop any significant lung lesions, while all of the animals exposed to quartz developed granulomas and some frank fibrosis. Apparently, it takes more than three months but less than six months of continuous quartz exposure at 1 mg/m^3 to elicit an inflammatory response in the lungs, but longer than six months for a similar response in animals exposed to shale, even though the quartz levels were roughly equivalent. Additionally, the numbers of recruited PAM and PMN are persistent after six months of exposure and even increase when the insult is discontinued. This increase in cell numbers after discontinuation of exposure suggests release from a macrophage-leukocyte recruitment inhibition. The release of lytic enzymes form PAMs and PMNs into lung parenchyma is one mechanism that could explain the presence of fibrosis. However, we currently have no information about the functional capacity of these cells. We intend to investigate this very important aspect of the injury-repair mechanism in future work. After the 12 months of inhalation, the fibrogenic action of quartz alone was emphasized by the observation of silica-positive granulomas in the quartz-exposed animals when no similar lesions were observed in shale-exposed animals.

Autopsy data acquired by Seaton et al., on Scottish shale miners demonstrates increased incidence of both pneumoconiosis and neoplasia following decades of occupational exposure to native shale dusts (5). We also have data from lifetime, high-concentration inhalation and intratracheal instillation experiments in which fibrosis and tumors were observed in shale-exposed rats (6). We are continuing our efforts to understand the progression and specific nature of the toxicity of shale dusts as well as the responses of specific cell types involved in disease processes.

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THE EFFECTS OF HYDROGEN SULPHIDE ON EXCITABLE TISSUES

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Abstract

Hydrogen Sulphide (H_2S) and its solution ions (mainly HS^-) have been investigated with regard to:

1) Effect of H_2S and HS^- on the axonal sinal transport in the sciatic nerve of Rana Pipiens. Significant effects, such as changes in nerve conduction velocities are shown with both. However, significant differences in initial mode of action seem to indicate a transport through the tissues of H_2S in preference to HS^-. The effect of CN^- have also been investigated and an obviously different mechanism is indicated.

2) Effects of HS^- on the Rectus Abdominus muscle of Rana Pipiens. In particular an increase in tension upon stimulation with acetylcholine and inability to relax to the same extent as muscles which have not been treated is shown.

3) Some studies indicating the Ca^{2+} forms a tight ion pair with HS^- have been performed. Since Ca^{2+} mediates both axonal transport and muscle contraction relaxation the importance of this finding will be discussed.

All the above studies were conducted in isotonic solutions buffered to a typical body pH (7.4). The second and third study in particular yield results at concentrations of reagents closely matching realistic physiological concentrations in cases of exposure.

Résumé

Le sulfure d'hydrogène (H_2S) et ses ions en solution (principalement HS^-) ont été analysés quant aux:

1) effets du H_2S et HS^- sur l'acheminement de l'influx nerveux le long de l'axone dans le nerf sciatique de la grenouille (Rana Pipiens). Des effets significatifs, tels des changements dans la vitesse de conduction nerveuse se sont manifestés avec les deux produits. Cependant, des différences importantes dans le mode initial d'action

semblent indiquer un transport vers les tissus de H_2S de préférence à HS^-. L'étude de l'effet de CN^- a clairement indiqué un mécanisme différent.

2) effets du HS^- sur le muscle rectus abdominus de Rana Pipiens. Spécifiquement, l'augmentation de la tension à la suite d'une stimulation avec de l'acétylcholine et l'incapacité de relâcher le muscle dans la même mesure que les muscles qui n'ont pas été traités sont démontrées.

3) certaines études indiquant que Ca^{2+} forme une paire stable d'ions avec HS^- ont été effectuées. Etant donné que le Ca^{2+} intervient à la fois dans le transport au niveau de l'axone et dans la contraction/relaxation musculaire, l'importance de cette constatation sera traitée.

Toutes les études précédentes ont été effectuées dans des solutions isotoniques tamponnées à un pH typique du corps (7.4). Les deuxième et troisième études en particulier donnent des résultats à des concentrations de réactifs étroitement apparentées à des concentrations physiologiques réelles d'exposition.

Introduction

Hydrogen Sulphide (sulphide henceforth) is a toxic agent of wide distribution. A NIOSH (1) report lists over seventy occupations ranging from sewer cleaners to heavy water plants, from farmers to people working in fish processing plant, where exposure can occur.

The gaseous nature and the extreme toxicity of sulphide, often compared to hydrogen cyanide (cyanide henceforth) in potency, makes it a very serious health hazard.

In the past, it was widely held that the mode of action of sulphide was similar to cyanide (2) i.e. they both were assumed to be cytochrome oxidase inhibitors. While sulphide is indeed a temporary cytochrome oxidase inhibitor, recent work by Nicholls (3) shows that more than one sulphide per cytochrome oxidase unit is needed to block the respiratory function of the oxidase, further detoxification is relatively fast.

Chemically comparing cyanide and sulphide is untenable since cyanide is one of the most thermodynamically stable entities known. Cyano-methemoglobin is a well known hematologic standard used to calibrate spectrometers and has a shelf life of years. Sulphide in contrast is extremely labile even as the solid and reacts even more rapidly with any oxygen present when in solution.

As we have shown (4), (Figure 1) sulphide reacts with oxygen in the presence of various forms of heme (oxyhemoglobin, methemoglobin) at such a rate that a 20 minute half life is the most that can be expected from even a very high concentration of sulphide. A series of studies as yet unpublished clearly shows this to hold in the case of whole blood as well (Figure 2).

The mode of action of sulphide and cyanide are quite different even when judged from the standpoint of symptoms. Compare for example the olfactory paralysis above 350 ppm for sulphide and the well known knock-down effect of 1000 ppm or more of sulphide, which is always accompanied by apnea, with the hypernea typical of 1000 ppm of cyanide.

The combination of very different chemical character and stability with widely different symptomology makes it highly improbable that the toxic mode of action of the two substances should be the same.

Indeed reference to published work, as well as to some of our own work, has shown that the nitrite treatment, while an excellent treatment for cyanide, is at best ineffectual and at worst contraindicated for sulphide victims (4).

Previous in-vivo testing (5) indicates that sulphide has a strong influence on both central and peripheral nervous systems. As a logical follow up to this a program of in-vitro testing of excitable tissues was undertaken with a view to establish if any of the toxic properties of sulphide are due to interaction with these tissues.

The axonal transport of nerve impulses is an experimentally well established technique believed to be relatively insensitive to inter-species differences. Thus the first series of studies concentrated on the modification of axonal transport of signals in the sciatic nerves of "Rana pipiens" when these nerves are exposed to sulphide or cyanide.

Sciatic nerves from "Rana pipiens" were electrically stimulated, then exposed to various concentrations of either cyanide or sulphide solutions (pH 7.4 amphibian ringer solution) (6) or sulphide and cyanide gas (7). A clear difference between the mode of action of cyanide and sulphide is again manifest. (Figures 3,4,5,6). The following points are fully explained in published work (6,7) and are tabulated here for continuity and clarity of argument.

1. Cyanide acts as expected of a cytochrome oxidase inhibitor. Energy dependent nerve characteristics such as compound action potential (CAP) and conduction velocity (CV) gradually deteriorate, (i.e. decrease in potential and slowing down in conduction velocity) as the stored ATP reserve is used up by repeated stimulation. Not all the

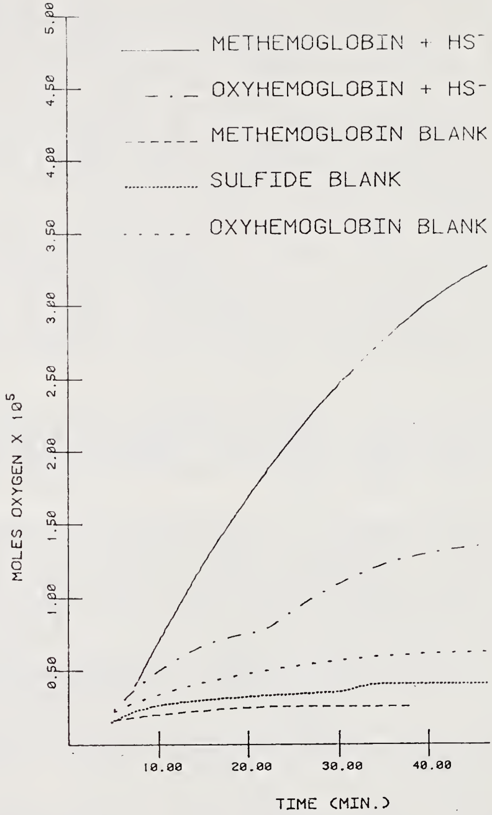

Figure 1: Met-hemoglobin and Oxyhemoglobin Concentrations are Equal. Sulphide Concentration is the Same in All Cases

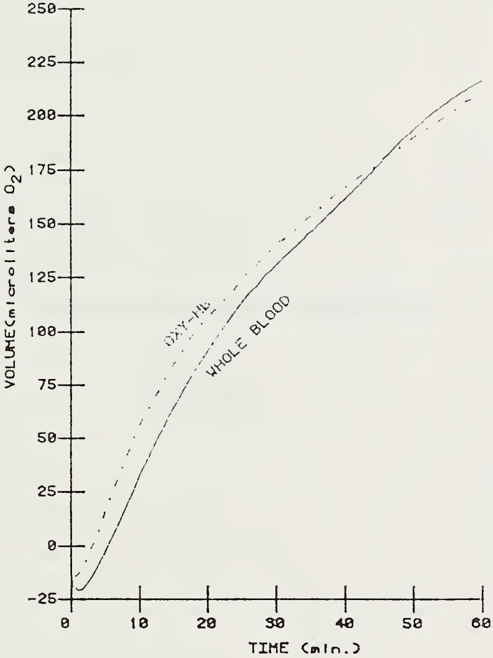

Figure 2: Oxyhemoglobin Concentration is the Same as Whole Blood Concentration

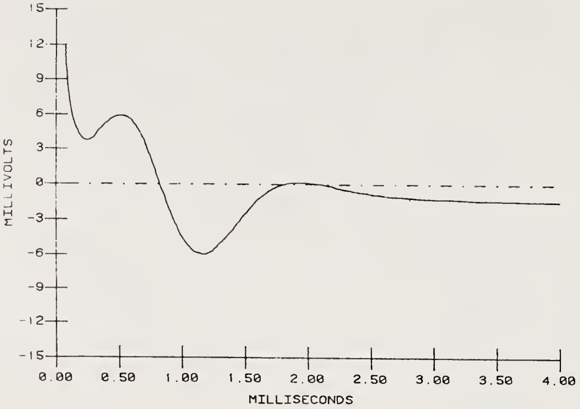

Figure 3: Sciatic Nerve Before Cyanide Treatment

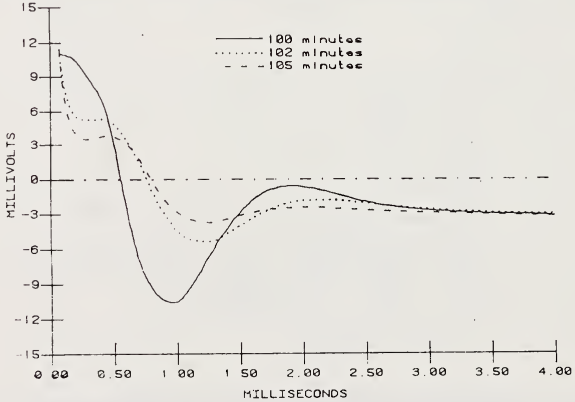

Figure 4: Sciatic Nerve after Cyanide (120 sec 10^{-1}M)

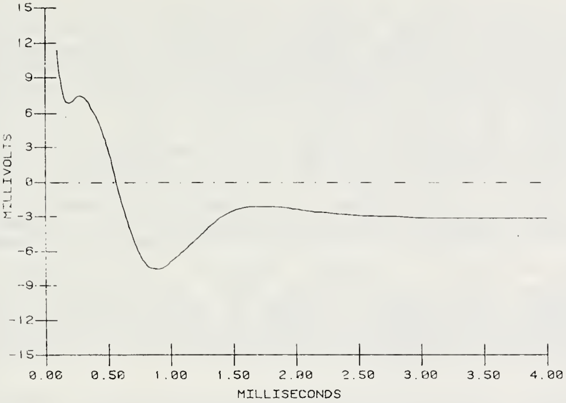

Figure 5: Sciatic Nerve Before Sulphide Treatment

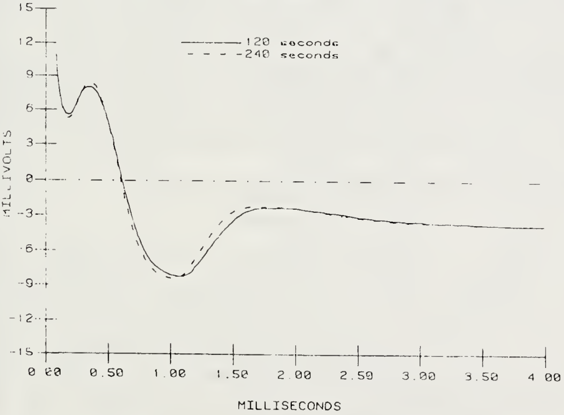

Figure 6: Sciatic Nerve after Sulphide (120 sec 10^{-2}M)

cytochrome oxidase is usually inhibited and the inhibition is to some extent reversible. A rest period without stimulation while the nerve is immersed in an oxygenated ringer solution allows the restoring of the ATP reserves. The nerve will then be active again for a period dependent on cyanide concentration and duration of rest.

2. Exposure to sulphide solution (i.e. 30% H_2S, 70% HS^- relative composition at pH 7.4 in an amphibian ringer buffer) increases the CAP to above the pre-exposure limit. No decrease of response on multiple stimulation was observed in clear contrast to cyanide. The increased CAP is still visible after 24 hours, the maximum workable length of time for a fresh nerve excised from other tissues.

   Since our work on sulphide oxidation indicates that no sulphide should be left in the nerve after one hour post exposure, some permanent change in nerve characteristics must have taken place on exposure. Other work seems to indicate (8) that some of the surfactants in the myelin sheath might be affected.

3. Sulphide in the gaseous phase (i.e. H_2S) has an immediate anesthetic effect, as expected because of its lipid solubility. Upon recovery from the anesthetic effect (i.e. complete cessation of responses to stimuli), typically 10 to 120 seconds depending on concentration of sulphide, the same effects as for the sulphide solution are observed. But for the extremely high concentration of H_2S (about 15,000 ppm) necessary to induce the anesthetic effect this would be a good explanation for the knock-down effect. At any rate, sulphide gas should never reach the nerve but rather the nerve will be bathed in body fluids containing sulphide, i.e. sulphide in solution which is 30% H_2S and 70% HS^- at pH 7.4. The gaseous work was done to yet more firmly establish the difference between sulphide and cyanide. This was accomplished as shown in point 4.

4. Cyanide gas behaved as cyanide solution except at very high concentration when function ceased and did not recover at all within the 24 hour workable period.

Thus it seems that any comparison between sulphide and cyanide is completely unwarranted on chemical, symptomatic and biochemical grounds. During the previous work on axonal nerve conduction, a dependence on Ca^{2+} concentration in the ringer solution was noted. Since Ca^{2+} is well known to have an important role in nerve and muscle response mechanisms, the possibility of an interaction between Ca^{2+} and HS^- was investigated. Table 1 indicates the result of a study on partition coefficients of HS^-/H_2S between an aqueous and an organic phase in the presence or absence of Ca^{2+} ions. It is evident that at pH 7.4, which is physiologically relevant as well as being near the pK_a (7.1) of H_2S so that both H_2S (oil soluble) and HS^- (water soluble) are present, the partition coefficients are influenced by the presence of Ca^{2+} in the aqueous phase. Interaction between HS^- and Ca^{2+} is thus established, possibly through a tight ion pair formation mechanism. The biological significance of this interaction to the availability of Ca^{2+} in the physiological system is now under investigation and it appears to be a promising lead to some of the observed effects of sulphide.

Recently completed work on the abdominus muscle of "Rana pipiens" also indicates a strong interaction between sulphide and the acetylcholine receptors responsible for muscle contraction.

Table II shows some summarized results. All work was done with the muscle in an isometric configuration using a Narco Bio-system F-60 strain gauge. Amphibian ringer is used throughout and the acetylcholine is removed by repeated washings.

TABLE I: Sulphide Concentration (M x 10^4) in the Aqueous Phase
Initial Sulphide = 3.47 x 10^{-4}M

	pH	No. Ca^{2+}	Ca^2 Present*
Set 1 (No oil)	6.0	3.32 ± .18 (4)**	3.22 ± .08 (4)
	7.4	3.23 ± .14 (3)	3.29 ± .09 (3)
	9.0	3.36 ± .20 (5)	3.46 ± .17 (5)
Set 2 (Nujol)	6.0	1.93 ± .11 (9)	1.78 ± .10 (8)
	7.4	2.51 ± .05 (9)	2.85 ± .14 (8)
	9.0	3.33 ± .11 (9)	3.39 ± .18 (5)
Set 3 (Corn oil)	6.0	1.30 ± .16 (5)	1.23 ± .09 (5)
	7.4	2.06 ± .16 (5)	2.26 ± .10 (5)
	9.0	2.76 ± .10 (5)	2.79 ± .17 (5)

Concentration = 1.08 x 10^{-3}M.

** ( ) = number of determinations.

TABLE II: Effects of Sulphide plus d-Tubocurarine

Run #	Order of Exposure	Recovery
1	Tubocurarine only	44%
2	Tubocurarine, sulphide	30%
3	Concurrently	4%
4	Sulphide, Tubocurarine	57%

Note - all recoveries are:
a) % of untreated muscle response
b) taken 2 hours after exposure

Worthy of note are the following features of the sulphide/muscle interaction:

a) Sulphide by itself does not effect the muscle under any concentration or exposure length.

b) Concurrent exposure of the muscle to acetylcholine and sulphide does not alter normal muscle response within the excitation/relaxation time sequence (2 to 5 minutes).

c) Exposure to sulphide alone results in an increased response to subsequent acetylcholine doses. This sensitization varies with concentration of the sulphide exposure and the length of exposure.

d) The sensitized muscle takes longer to relax after acetylcholine is washed off. In fact, some muscles never relax.

e) The sensitized muscle is more sensitive to subsequent sulphide exposure. In particular, the addition of sulphide and acetylcholine will yield a higher response than acetylcholine alone. According to (b) this synergic effect is not present in the unexposed muscle.

Table III clearly shows a synergic effect of sulphide with a well known muscle response inhibitor (tubocurarine) which is known to act at the acetylcholine receptor sites.

Table II, points (a) through (e) and Table III strongly indicate that exposure to sulphide modifies the acetylcholine receptor sites in muscle. The modification appears to be irreversible over the 20 to 24 hours usable period of muscle in vitro. If true in vivo, this modification would represent a sensitization route which should be explored in the context of chronic rather than acute exposure. However, in view of required time and concentrations, these muscles effects are probably not responsible for the characteristic knock-down effect of acute exposure.

TABLE III: Direct Agonist Effect of Hydrogen Sulphide

t(hours)	Tension	Delta-T
1	124%	182%
4	–	175%
18	161%	156%
20	–	126%

Many of the effects of H_2S poisoning, notably the central respiratory paralysis concommitant with "knock-down" are also evident in the case of organo-phosphate exposure at higher concentration (9). These organo-phosphates are known to be acetylcholine esterase inhibitors. A start has been made in investigating the possible inhibitory effects of sulphide. Preliminary results indicate a thirty percent inhibition of acetylcholine esterase using a 10^{-3} molar concentration of sulphide. Because of the labile nature of sulphide, numerous technical difficulties are present making these data only moderately ($\pm 10\%$) reliable. However, these are interesting numbers in a biological context. Much more work is necessary before this story is clear.

In conclusion the following points should be noted. This research strongly supports the contention that sulphide is not like cyanide since we see no similarity on chemical grounds. Indeed, this study reinforces the position taken by Sandhu et al. in the recommendation section of their excellent review (10).

Given the wide occurrence and the toxicity of sulphide, the present lack of reliable data and knowledge about the mode of toxic action of sulphide and its possible antidotes is dangerously unwise.

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THE GENOTOXIC EFFECT OF EPICHLOROHYDRIN ON MICE AS ESTIMATED BY THE MICRONUCLEUS TEST

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Abstract

Chromosome breakage and malfunction of the spindle cell apparatus result in bodies termed micronuclei. The majority of these appear in the young erythrocytes. Increase in their number has been used as an indication of mutagenic activity. They appear in significant numbers in the blood of mice treated with clastogenic chemicals. The procedure was used in assessing the mutagenicity of epichlorohydrin (ECH). Mice injected 12 times in 16 days with ECH showed significantly increased numbers of micronuclei (MN) in the normochromatic erythrocytes (NCE) 8 days following treatment. Increasing numbers of polychromatic erythrocytes (PCE) in the peripheral blood, the weight gain, and the numbers of nucleated cells in the bone marrow were not affected.

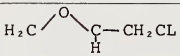
Résumé

Rupture de chromosomes et défectuosité de la formation fuseauriale de la cellule conduisant à la formation de corps appelés micronuclei. La majoritié apparaissent chez les jeunes érythrocytes. Une augmentation de leur nombre est reconnue comme une indication d'activité mutagène. Ils apparaissent en nombre significatif dans le sang de souris traitées avec des produits chimiques clastogènes. Cette méthode a été utilisée pour évaluer l'effet mutagène de l'épichlorhydrine (ECH). Les souris auxquelles on a injecté du ECH 12 fois en 16 jours ont montré une augmentation significative du nombre de micronucléi (MN) dans les érythrocytes normochromatiques (ENC) 8 jours suivant le traitement. Un nombre accru de ces cellules apparaît au cours des 11 jours qui suivent. Le nombre des érythrocytes polychromatiques (EPC) dans le sang périphérique, le gain de poids, et le nombre de cellules avec noyau dans la moelle épinière n'étaient pas affectés.

Introduction

Epichlorohydrin is an epoxy (containing low molecular weight) compound of unusual chemical activity having two functional groups. Its properties are summarized in Table I. Its production exceeds 300 million pounds annually. It is used in the manufacture of epoxy resins, surface active agents, coatings, glycidyl ethers, textiles and insecticides.

TABLE I: Epichlorohydrin (ECH) - Chemical and Physical Data

Chemical Formula	
CAS	Chloromethyl Oxirane 106-89-8
Boiling Point	116.2 C
PEL (USA)	2 mg/m^3 (0.5 ppm) - 40 hrs. 19 mg/m^3 (5 ppm) - ceiling
Reactivity	with Active Hydrogen Compounds

A number of studies have been conducted with the compound which define not only its toxicity (moderately toxic, highly irritating) but its mutagenicity as well.

In vitro microsomal metabolism studies by the Shell Development group at Houston Texas (Beatty, et al. and Gingelle et al.), indicated a total binding of 1.7 mmoles ECH/mg of protein. There was a rapid conversion of ECH to a chlorohydrin (ACH) and glycidol (GCD), the latter compound being formed primarily by nonenzymatic conversion of ACH. Rats administered C-14 tagged ECH exhaled 38% of the dose as CO_2. Fifty percent was excreted as metabolites in the urine and 3% in the feces. The remaining 9% was in the tissues.

The principal urinary metabolites identified were; N-acetyl-5-(3 chloro-2-hydroxypropyl) L-cysteine (35%), and 5% alpha-chlorohydrin (Figure 1).

The purpose of this study was to determine if a procedure which was relatively simple to perform, of short term, inexpensive, not requiring a high degree of technical skill, and using an intact animal could be used to predict effects on DNA and therefore mutagenicity. To this end, we chose the micronucleus test.

Chromosome breakage and malfunction of the spindle cell apparatus will result in the incorporation of small particles of chromatin in daughter cells, where these can fuse with the nucleus or form one or several nuclei. Because of their small size, they are referred to as micronuclei (MN). These appear most frequently in the various cells of the bone marrow, a great majority of them being in the young erythrocytes (1). Increase in their number has been used as an indication of mutagenic activity (2 - 4).

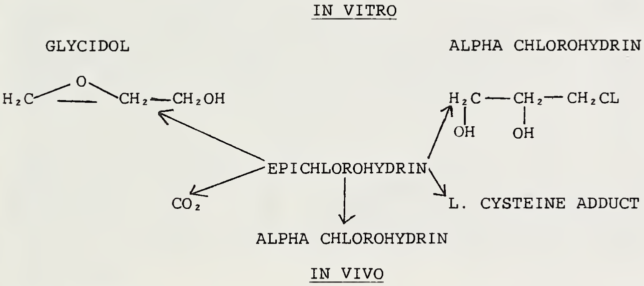


Figure 1: Biotransformation of Epichlorohydrin

Recently, MacGregor, et al. (5) demonstrated that these (MN) would appear transitorily in the peripheral blood of mice treated with clastogenic chemicals. In 1982, Schlegel and MacGregor (6) demonstrated persistence of these micronuclei up to forty days following repeated injections of test plastogens.

In our study, we assessed the mutagenicity of epichlorohydrin (ECH) using the appearance of MN in the peripheral blood of mice receiving repeated injections of the chemical as the indicator.

Material and methods

Cyclophosphamide (C.P. Neosar - manufactured by ASTA - Werke A.F., Bielefeld, Germany, lot 711000881); ECH supplied by Shell Development Company, 99.9%; and corn oil (CO) (Mazola) typical of food grade oil, were used.

Male Swiss-Webster weanling mice (Simonsen Laboratories, Gilmore, CA) 15-17 grams starting weight were used as the test animals. The positive control was CP; the negative control CO. The mice were injected intraperitoneally on days 1 - 5, 8 - 12, and 15 - 16 for twelve doses given over sixteen days. CP and

ECH were administered at doses of 22 and 10 mg/kg respectively in a volume of 10 mg/kg of sterile isotonic saline or corn oil. The corresponding control group received injections of corn oil in the same volume. The CP was used within six days after dilution and the CP solution was stored in the refrigerator. The ECH was prepared freshly prior to each time of injection, and was kept in an ice bath prior to injection.

There were six mice in each group. Peripheral blood smears were taken from the ventral tail vessel of each mouse on days 6, 8, 13, 15, 17 and 19. Approximately 10 µl of blood was used and smears made according to the method of Schlegel and MacGregor (6). The frequency of micronucleated NCE and percent of polychromatic erythrocytes (PCE) were determined. The incidence of micronucleated NCE was counted in 1000 NCE from each sample except that of the ECH group. In the ECH group, two mice died within four days after the start of the injections, so that 2000 NCE were counted from each sample of this group. After the final preparation of blood smears, animals were killed, femurs disarticulated and the total number of nucleated cells in the bone marrow determined by the method of Gerarde (7). The mice were weighed prior to each injection and at the conclusion of the experiment. A single tail t-test was used for statistical analysis.

Results and Discussion

The frequency of micronucleated NCE in the positive control CP treated group showed an expected significant increase over the negative control values on day six, the first sampling date ($P<0.05$). Thereafter, the number of micronucleated NCE increased on successive days reaching a frequency of 13.3/1000 NCE, ($P<0.001$), on day 19 (Table II).

TABLE II: Incidence of Micronuclei (NCE) in Peripheral Blood

Day	Test Group		
	ECH	CPP	CO
1			1.0
6	2.4	3.0*	1.7
13	3.3*	5.7*	1.7
19	5.2*	13.5*	0.1

In the group treated with ECH, the number of micronucleated NCE/1000 NCE were not elevated significantly until day eight, when a mean value of 3.1/1000 NCE $P<0.001$, was obtained. Thereafter, the mean value increased continuously, reaching the value of 5.2/1000 NCE on the last day. The numbers of the PCEs in both test groups were not significantly decreased in any sample at any time, except for the group treated with CP on the sixth day. There was no obvious suppression of erythrocyte production with any of the treatments.

The values for total nucleated bone marrow cells counts in CO, CP and ECH groups were: $(3.13 \pm 0.12) \times 10^7$; $(2.48 \pm 0.06) \times 10^7$; and $(2.23 \pm 0.13) \times 10^7$ per femur respectively. There was a significant decrease of total nucleated bone marrow cell count only in the CP group ($P<0.001$). These results demonstrate that there is some suppressive effect of cyclophosphamide production of bone marrow cells at the dose tested. Decreased weight gain was noted only in group CP. Table III.

TABLE III: Results of Study

Measurement	Difference from Negative Control	
	Positive control	Epichlorohydrin
Body Weight	0	0
Bone Marrow Count	0	0
Numbers of MN	+	+
Numbers of PCE	0	0

Discussion

ECH has been demonstrated to have mutagenic activity in micro-organisms and in drosophila, but not in the dominant/ lethal assay in the mouse. Chronic toxicity evaluations have indicated that ECH, while not being a skin carcinogen in the mouse or rat, does cause increase in squamous cell carcinoma in the nasal cavity among other tumors. ECH is also a suspect respiratory carcinogen in humans, based on epidemiological studies. It has been demonstrated that there has been no suggestion that there is a depression of sperm count in males with long industrial exposure, although reversible infertility has been shown in male rats (8) (Table IV).

The results of this experiment indicate that epichlorohydrin is a clastogen producing micronuclei in peripheral blood erythrocytes of the mouse. Because of the short duration of the test and the ease with which it is performed, measurement of micronuclei appears to be an excellent tool for evaluation of the possible clastogenic properties of chemical compounds. Unfortunately to date, these data are not reproduceable in species other than the mouse, and it has not been possible to monitor humans exposed to this product by this technique.

TABLE IV: Mutagenicity Studies - Epichlorohydrin

Test System	Results
Host - mediated assay (Salmonella strains TA 100, TA 1950)	+
Cultured mammalian cells	+
Transplacental mutagenicity	+
Human bone marrow	+
Sex-linked recessive lethal mutations - drosophila	-
Germ cells - mice	-
Micronuclei - mouse bone marrow	-

Summary

Mice injected 12 times in 16 days with epichlorohydrin (ECH) showed significantly increased numbers of micronuclei (MN) in the normochromatic erythrocytes (NCE) eight days following treatment. Increasing numbers of these cells appeared during the next eleven days. The number of polychromatic erythrocytes (PCE) in the peripheral blood, the weight gain, and the numbers of nucleated cells in the bone marrow were not affected.

The micronucleus test appears to be a satisfactory procedure for determination of possible mutagenic effects of chemicals, since it correlates well with other experimental procedures indicating mutagenicity.

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THEME II

EMERGENCIES IN THE CHEMICAL INDUSTRY: ASSESSMENT AND INTERVENTION

URGENCES DANS L'INDUSTRIE CHIMIQUE: EVALUATION ET INTERVENTION

EMERGENCIES IN THE CHEMICAL INDUSTRY: ASSESSMENT AND INTERVENTION

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Preface

The topic "Emergencies in the Chemical Industry: Assessment and Intervention" obviously features largely in our daily work and has been discussed at national and international congresses worldwide in recent years. Here are just a few conferences where the subject has been discussed:

- Seminar on the "Organization of Resuscitation and Casualty Services", held in Leningrad, U.S.S.R., in July 1967.
- International Congress of Disaster Medicine, held in Mainz, F.R.G., in October 1977.
- Medical Conference on "Preventing an Atomic War", held in Hamburg, F.R.G., in September 1981.
- "Atomic Explosion - Disaster Control Medicine", International Congress held in Amsterdam in June 1983. On this occasion, U.S. President Reagan and U.S.S.R. President Andropov sent greeting telegrams.

Especially in the F.R.G., this important issue, which every physician is confronted with, has been discussed in a great number of papers:

- "The medical consequences of a thermonuclear war", Deutsches Arzteblatt (DA), volumes 8,9,10,11 and 12/1965.
- "Disaster control medicine and medical care in civil defense - including nuclear power emergencies", IVth Interdisciplinary Forum of the German General Medical Council, January 1980, Yearbook 1980/81: "Fortschritt und Fortbildung in der Medizin", Deutscher Arzteverlag, Köln, 1980.
- "Disaster control is part of social security - Switzerland is well prepared", report in DA 38, Sept. 18, 1980.

After this introduction, my paper will be split up into 3 parts:

i. General comments.

ii. Personal experience (disaster control in the chemical industry in the light of company arrangements and legislation).

iii. Conclusions - Recommendations - International Cooperation.

General comments

Definition

The Executive Board of the World Health Organization has defined disasters or "emergencies" as situations where there are unforeseen serious and immediate threats to public health. Particularly severe disasters may be classed as catastrophes; such occurrences, whether natural or man-made, disturb or overthrow the existing order. (Bauhofer, F.A.: Types and Events of Disasters. WHO, International Congress on Disaster Medicine, Mainz, F.R.G., October 30, 1977).

In the Encyclopaedia of Occupational Health and Safety, Volume I, Third Edition, 1983, the definition of a disaster is given on page 652:

> "A disaster is a catastrophic situation in which the day-to-day patterns of life are, in many instances suddenly, disrupted and people are plunged into helplessness and suffering and, as a result, need protection, clothing, shelter, medical and social care and other necessities of life".

Catastrophes as defined above are by no means typical merely of the age in which we are living. There have been catastrophes in all ages. The word "catastrophe", which comes from Greek and means the "overturning" of normal regular events, "a turn for the worse", is unfortunately frequently misused. For example, in order to make an impression or cause a sensation, the word "catastrophe" is even used to describe critical situations, for instance in the family sphere or in political and even economic contexts. The word "catastrophe" should be used carefully, and it is therefore wise to use this term only in circumstances where there has been an emergency which threatens to spread, and local relief organizations are no longer able to cope with it successfully using their own resources. A catastrophe is the last and most serious link in a chain of accidents.

Over the years, many different catastrophes have happened all over the world as the result of war, natural occurrences, transport accidents, explosions, poisoning, etc. In "International Management", London, April 80, it is stated that "although occurrences of catastrophes have increased throughout this century in proportion to increased industrialization, the number of resulting fatalities has diminished".

Catastrophes and major accidents may have the same causes as near accidents and slight or serious accidents. Protection against accidents is therefore primarily a question of preventing accidents. Protection against catastrophes: protection against accidents and analysis of dangers = risk estimate.

General planning for disaster control

One of the main tasks of a plant physician in the chemical industry is planning measures to be taken by a medical department in the event of a disaster. All disasters bring in their wake similar consequences that call for immediate action, whether at the local, national or even international level.

If a disaster happens, there are two phases calling for the plant physician's action:

the emergency phase - immediately after the disaster happens, and

the rehabilitation/reconstruction phase - in which the stricken communities have to deal with the resulting problems.

Planning for disaster control should be carried out well in advance and in collaboration with the company's safety department, representatives of the employer and the employees, the company's fire department, the company's welfare service and medical department, the community, especially physicians and medical personnel in the area, and, if necessary, military-medical personnel, and the local police.

Pre-disaster planning is a necessity and has to be dealt with under two headings:

- preparedness and

- prevention.

On page 653 of the Encyclopaedia of Health and Safety it is stated: "...preparedness covers all action taken with a view to organizing and facilitating timely and effective rescue, relief and rehabilitation in cases of disaster ..." and: "Prevention means the formulation and implementation of long-term policies and measures to mitigate the impact of natural phenomena on human settlements, and on economic and social development as a whole".

Legal requirements for the orderly planning of disaster preparedness and relief operations already exist at varying levels of competence and authority in a large number of countries. It is important that the guidelines relating to pre-disaster preparedness should provide for coordination and define the respective roles and responsibilities of the various authorities.

The ILO Encyclopaedia states that "...pre-disaster activities must start with the identification of disaster-prone areas and the types of event: they should continue with provisions for public information and the establishment of early-warning systems, training of personnel in rescue, making special stand by arrangements with customs authorities and internal transportation companies for the rapid clearance and channeling of relief supplies to disaster sites and distribution to the survivors, stockpiling of relief equipment, medicines, and simulation exercises to test the efficiency of the plan. When a disaster occurs, rescue and relief operations can thus be initiated without delay. The magnitude of a disaster must be quietly ascertained.

As the initial emergency period comes to an end, attention has to turn towards repair and reconstruction work. Priorities and needs will vary greatly depending on the type of disaster: accident analysis comes first; prevention of a second disaster and repair and reconstruction work will follow.

When a full reconstruction programme has been developed, it may be found useful to introduce training in new techniques, and pay attention to the special problems of the newly disabled.

Personal experience

BASF Aktiengesellschaft, Ludwigshafen am Rhein, Federal Republic of Germany, comprises 300 different production units and over 1,600 separate buildings covering an area of about 6.5 sq. km. Over 50,000 employees manufacture some 6,000 products and 12,000 intermediates.

During it's 117 year history, BASF Aktiengesellschaft has suffered two disastrous explosions. The most recent one was in 1948, when a rail tanker containing dimethyl ether ruptured. The resulting cloud of vapor (July 27, 1948 was a very hot day) exploded, killing 207 workers and injuring a number of people outside the perimeter of the plant. As the result of the excellent cooperation between all the divisions, institutions, rescue teams and the Occupation Forces, the rescue and relief measures were exemplary.

Since then, even greater importance has been attached to planning for emergencies. The plans cover both major and minor dangerous occurrences. It is stated in the Guidelines for Occupational Safety (issued by the BASF Board of Executive Directors): "Productivity and profitability must be subordinated to safety..." and, elsewhere, "... the necessary operating and safety instructions as well as emergency measures must be laid down in writing...".

For BASF Aktiengesellschaft in Ludwigshafen, planning the successful deployment of medical services means the harmonious integration of all the necessary measures into an overall plan involving the company's Safety, Welfare and Fire Departments, local doctors, and hospital personnel and, if necessary, military medical units in the area.

Disaster control planning particularly for the medical services will be explained with reference to the seminar of the Medical Society held in Ludwigshafen on May 5, 1982 and the practical experience obtained in an emergency exercise on November 11, 1982. The seminar was attended by some 300 doctors from Ludwigshafen and the vicinity.

The title of the scientific seminar was "Precautions and measures for accidents in big chemical companies". The various papers were as follows:

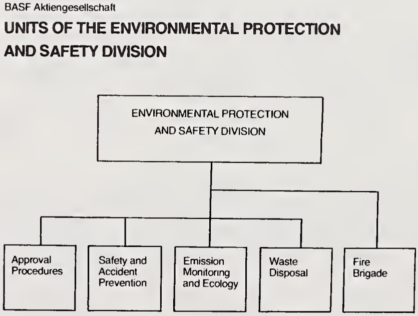
1. Fritsche, D.: Introduction to the subject
2. Tischbein, K.H.: Operations planning for protection against hazards as the responsibility of the town of Ludwigshafen am Rhein
3. Peine, H.G.: Procedures to be followed in the event of dangerous occurrences with reference to BASF
4. Stahl, H.: Approval procedures for chemical plants
5. Häberle, M.: Immission after accidents
6. Knies, H.: Measures for preventing accidents
7. Thiess, A.M.: Deployment of medical services in the event of an accident
8. Nimptsch, P.: Averting dangers in a big chemical company
9. Arens, W. and Kopp, K.: Operations planning in hospitals in the event of major accidents
10. Paul, M.: Possibilities of the Federal Defence Forces providing medical assistance in major emergencies in industry.

The Mayor, Mr. K.H. Tischbein, who is responsible for public health, stated in his paper entitled "Operations planning for protection against hazards as the responsibility of the town of Ludwigshafen am Rhein" that both the Constitution (Article 35) of the Federal Republic of Germany and that of Rhineland-Palatinate (Article 111) specify measures to be carried out in the event of a disaster. The local authorities and rural districts are responsible for planning operations in the case of disasters. According to Section 4 of the Firefighting and Disaster Control Act of Rhineland-Palatinate, the town of Ludwigshafen is obligated to prepare alarm and operations plans for major hazards and keep them up to date. The operations plan deals with a total of 12 possible dangerous occurrences, e.g. large fires, explosions, serious road traffic accidents, and air accidents. Flexibly designed, the operations plan has already passed some tests. The town has concluded an "Agreement on measures to be taken in the event of hazards and accidents in chemical plants" with the chemical companies. This agreement, known as the "Ludwigshafen Model", which was the only one of its kind in the Federal Republic of Germany when it came into effect in July 1980, ensures that the municipal authorities and all other competent authorities and institutions are informed promptly of any occurrences. An emergency leaflet was also drawn up for the population containing straightforward information (in seven languages) on what to do in the event of a major emergency.

H.G. Peine spoke on "Procedures to be followed in the event of dangerous occurrences with reference to BASF". In the event of such an occurrence at BASF's Ludwigshafen plant, all units of the Environmental Protection and Safety Division are involved (Figure 1).

These units are:

- Approval procedures
- Safety and accident prevention
- Emission monitoring and ecology
- Waste disposal, and
- Fire brigade.



BASF Aktiengesellschaft

UNITS OF THE ENVIRONMENTAL PROTECTION AND SAFETY DIVISION

ENVIRONMENTAL PROTECTION AND SAFETY DIVISION
Approval Procedures
Safety and Accident Prevention
Emission Monitoring and Ecology
Waste Disposal
Fire Brigade

Figure 1

All in all, the Environmental Protection and Safety Division employs 650 people. This unit is assisted, in the event of a major dangerous occurrence, by a Steering Committee with the following special departments (Figure 2):

- Public Relations
- Analysis
- Investigation of cause of accident
- Investigation of extent of damage
- Clearance work
- Legal

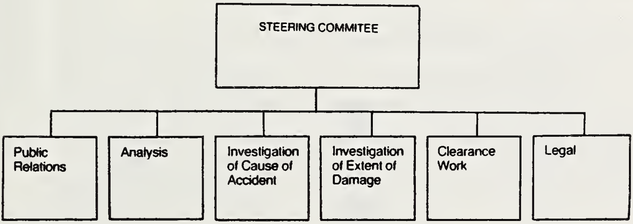

STEERING COMMITEE
Public Relations
Analysis
Investigation of Cause of Accident
Investigation of Extent of Damage
Clearance Work
Legal

Figure 2

If an accident occurs, the most important adviser is the manager of the plant concerned. The headquarters of the Fire Brigade has the addresses of 4-5 experts in the particular field for each plant. Of the units listed under the Steering

Committee, special mention should be made of the Public Relations Working Group. It is this group's responsibility to provide the media and thus the population with information right from the start. The emergency leaflet prepared in collaboration with the municipal authorities is distributed to households in the vicinity. In the event of any major accident, vehicles for monitoring emissions and (whether they are needed or not) ambulances turn out with the fire brigade.

As far as notification is concerned, it should be pointed out that the municipal and supervisory authorities are notified of an accident immediately. Frequently a precautionary notification is made, if a call for assistance gives the impression that a major occurrence is involved. If this proves to be a false alarm, a second message gives the "all clear" (Figure 3).

BASF Aktiengesellschaft

NOTIFICATION PROCEDURE FOR ACCIDENTS

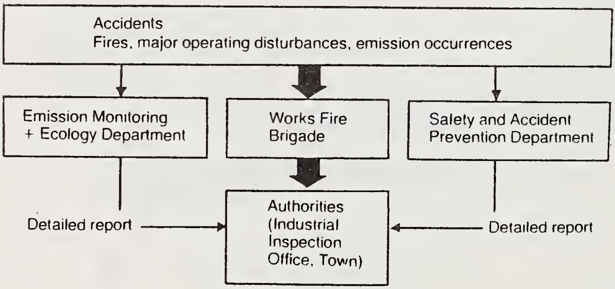

Accidents
Fires, major operating disturbances, emission occurrences
Emission Monitoring + Ecology Department
Works Fire Brigade
Safety and Accident Prevention Department
Detailed report
Authorities (Industrial Inspection Office, Town)
Detailed report

Figure 3

Attention should be drawn to the Federal Emission/Immission Protection Act in the Federal Republic of Germany, which was dealt with in H. Stahl's paper on "Approval procedures for chemical plants". The Act requires that, in plants that are subject to approval, humans, animals and plants should be protected from hazards that could be caused for example by fire or explosions. Twelve implementing regulations have been issued so far. The public must also be involved in the approval proceedings, and all chemical plants in which highly toxic or explosive materials are manufactured in considerable amounts are covered by the Accident Regulation that came into force in September 1980. All effects that may result from an accident must be notified to the authorities. The Safety Data Sheets published by BASF contain the most important data for a product's safety in lucid form. State regulation and bureaucracy have constantly expanded (see the following list).

Legislature in the environmental field - (Extract)

1852	Bavarian Water Utilization Act
1873	Industrial Code
1907	Bavarian Water Act
1956	Water Protection
1957	Water Management
1960	Water
1964	Air
1970	Storage of Water-Polluting Liquids Noise
1971	Lead in Gasoline
1972	Waste Disposal Waste
1973	Water-Polluting Substances
	Dangerous Goods Transportation
1974	Immission Protection
	Air Waste
	Cradle-to-Grave Manifesto
	Waste Imports
	Waste Transportation
	Environmental Statistics
1975	Furnaces
	Sulfur in Heating Oil
	Plants Subject to Approval
	Immission Control Supervisor
	Immission Control Supervisor
	Waste Water Harmfulness
	Dangerous Goods Transportation
1970	Waste Water Dues Act
	Smog
	Polluted Areas
1977	Approval Procedures
	Detergent Degradability
	Waste Disposal
1978	PCB, PCT and VC Limits
	Emission Inventory

1980 Chemicals Act
Accidents
Flammable Liquids
Dangerous Substances
Waste Water Dues Act
Environmental Offences Control Act

H. Knies spoke on "Measures for preventing accidents". Appropriate instruction and the motivation of all employees are of particular importance in this respect. Each employee joining a production plant is familiarized with the specific hazards and conditions in the plant (with the aid of interpreters in the case of immigrant workers). Later, regular instruction by superiors keeps knowledge at the necessary level. Safety competitions greatly motivate employees to reduce the number of accidents or prevent them completely.

P. Nimptsch, head of the Works Fire Brigade, talked about "Averting dangers in a big chemical company" and explained that the Works Fire Brigade was called out in the following circumstances:

- fires
- explosions
- products escaping
- accidents
- emergency situations, etc.

The BASF Fire Brigade has 180 members. The equipment meets the special requirements of a chemical plant.

All vehicles have radio and loudspeaker equipment with pre-recorded warnings on cassettes. The mobile operations center has an operations data bank recorded on microfilm and a viewer for the supply and removal of water for extinguishing fires, descriptions of all the buildings and index cards for breakdown and repair services. There is also a data bank containing information on a great variety of hazardous substances available in the Fire Brigade's communications center. According to the Fire and Disaster Control Act of Rhineland-Palatinate, the person in charge of operations in the event of a disaster is the head of the Environmental Protection and Safety Division.

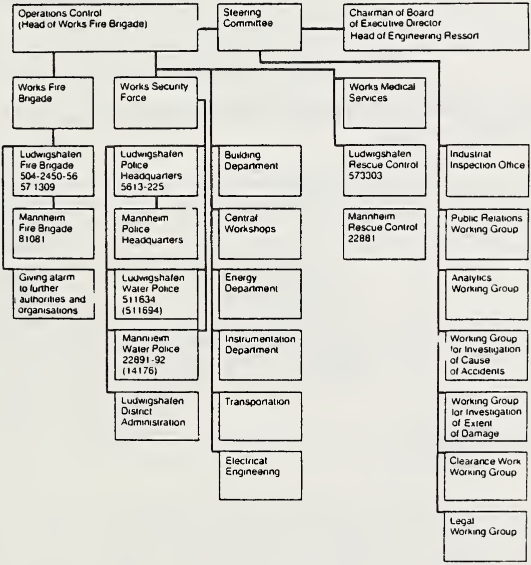
For 29 substances there are so-called alarm plans. The vicinity of the particular plant is divided up into zones and sectors.

Depending on the scope of the accident that has occurred, the following differentiations are made:

- Plant alarm
- Minor alarm
- Major alarm

To assist operations control in dealing with a dangerous occurrence, accident working groups were formed at BASF to handle air and water analysis, etc. in the event of an emergency. Each report to the authorities is made in coded form. Warnings are given to works employees and the population via radio broadcasts and air-raid sirens.

The "Alarm Plan for Special Dangerous Occurrences" shows the telephone numbers of municipal and supervisory authorities to be notified immediately (Figure 4).



Alarm Plan
for Special Dangerous Occurrences

Operations Control (Head of Works Fire Brigade)
Steering Committee
Chairman of Board of Executive Director Head of Engineering Ressort
Works Fire Brigade
Works Security Force
Works Medical Services
Ludwigshafen Fire Brigade 504-2450-56 57 1309
Mannheim Fire Brigade 81081
Giving alarm to further authorities and organisations
Ludwigshafen Police Headquarters 5613-225
Mannheim Police Headquarters
Ludwigshafen Water Police 511634 (511694)
Mannheim Water Police 22891-92 (14176)
Ludwigshafen District Administration
Building Department
Central Workshops
Energy Department
Instrumentation Department
Transportation
Electrical Engineering
Ludwigshafen Rescue Control 573303
Mannheim Rescue Control 22881
Industrial Inspection Office
Public Relations Working Group
Analytics Working Group
Working Group for Investigation of Cause of Accidents
Working Group for Investigation of Extent of Damage
Clearance Work Working Group
Legal Working Group

Figure 4

"Deployment of medical services" was my subject. According to Section 3.1 of the German Safety at Work Act, a plant physician is responsible for advising the employer on the organization of first aid in the plant. Section 55 of the Workplace Regulation obliges an employer to draw up an escape and rescue plan. Also laid down: "Practices must be carried out according to the plan at appropriate intervals to see how employees can reach safety or be rescued in the event of danger or a disaster". The plan of action in Figure 5 shows the deployment of medical services, embedded in the plan of action for all special services.

Operations plan of the occupational medicine and health protection department for the medical services

A special operations plan, which is reviewed and amended twice a year, lays down all the measures concerning the planning, organization, medical facilities, staff, etc.

PLAN OF ACTION FOR THE SPECIAL SERVICES IN THE EVENT OF MAJOR EMERGENCIES

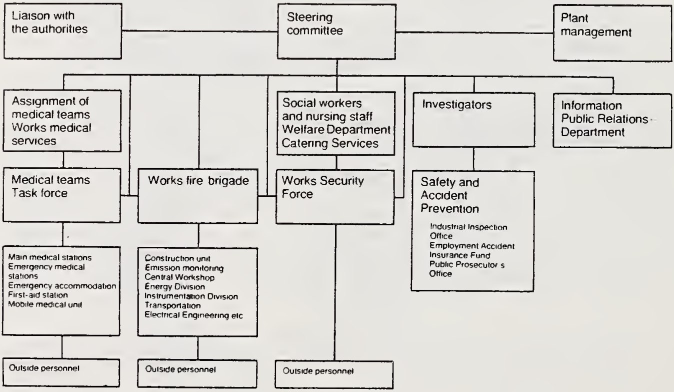

Liaison with the authorities
Steering committee
Plant management
Assignment of medical teams Works medical services
Social workers and nursing staff Welfare Department Catering Services
Investigators
Information Public Relations Department
Medical teams Task force
Works fire brigade
Works Security Force
Safety and Accident Prevention
Industrial Inspection Office
Employment Accident Insurance Fund
Public Prosecutor's Office
Main medical stations
Emergency medical stations
Emergency accommodation
First-aid station
Mobile medical unit
Construction unit
Emission monitoring
Central Workshop
Energy Division
Instrumentation Division
Transportation
Electrical Engineering etc
Outside personnel
Outside personnel
Outside personnel

Figure 5

Organization

Planning:

- Assessment of the emergency
- Tasks of the medical service
- Explanations of the operations plan
- Operation tasks (in keywords)
- Map material:

Map I	Overall view of the BASF plant
Map II	Medical facilities (within the BASF plant)
Map III	Ambulances and hospitals (outside BASF)

Personnel survey

- Plant physicians
- Male and female nurses
- Works medical personnel for the ambulances
- Auxiliary personnel (technical assistants and secretaries)
- Dentists, dental technicians, and assistants
- Staff of the Toxicology Department

Medical facilities - Material

within BASF:

- Medical stations South and North
- Emergency medical stations South and North
- Emergency accommodation (first aid stations)
- Ambulances

outside BASF

- Hospitals
- Telephone directory
- BASF extension lines to the following departments: Works Fire Brigade, Safety and Accident Prevention, Works Security Force, Transportation, Energy, Welfare, and Catering
- Examination certificates

Medical care and transportation of persons injured or suffering from poisoning

In the event of an emergency, self-help will initially have to be first aid. Therefore, for 25 years, we have seen to it that laymen and emergency medical personnel are trained carefully. Up to now, some 20,000 employees have received theoretical and practical first-aid training. More than 4,000 employees, e.g. those working with hydrocyanic acid or electricity, have been given special training.

Second aid will then be provided by plant physicians and trained medical personnel and, if necessary, they will be supplemented by non-BASF personnel. This aid also comprises the transportation of the injured, once they can be moved, in the necessary order of priority (triage). It is very important that every injured person is marked with an identification card (in triplicate) or bracelet showing the person's name, the severity of the injuries, and the medication received.

The self-help is immediately followed by aid from the rescue and ambulance services. The ambulance men will be at the scene of the accident first and support and supplement the first aid already rendered. The leaders of these "advance teams" will assess the scope and seriousness of the emergency. Their reports will be communicated by radiophone, telephone or messenger to those in control, who will decide what further action is to be taken.

Third aid will be rendered in hospitals in the neighbourhood and, if necessary, in relief hospitals of the German Red Cross, the Federal Defense Forces and the voluntary organisations (Figure 6).

FIRST AID	SECOND AID	THIRD AID
Scene of accident	BASF medical facilities (collecting points)	Hospitals Surgery Ward for serious burns and radiation injuries Intensive-care ward Detoxication ward Other special wards
Self-help (laymen) Rescue personnel (physicians and nurses, if necessary)	Plant physicians, etc. (specialists) Nurses and auxiliary personnel	Specialists Surgeons Internists Anesthetists Other specialists Information passed on to the specialists in cases of poisoning
Transportation and medical care in ambulances for those injured or suffering from poisoning		

Figure 6

Hospitals and medical facilities in the immediate vicinity and further away

Figure 7 shows all the hospitals and voluntary organisations in the vicinity of BASF. Over 300 beds are available in the event of an emergency. The telephone numbers and distances in kilometers are given. There are special telephone lines between BASF's Medical Department and the municipal hospital and the accident hospital of the Employment Accident Insurance Funds. A regular exchange of experience takes place between organizations.

Rescue and ambulance teams

The rescue and ambulance service consists of 26 trained employees who work in shifts. Particular attention is given to further training in specialized hospitals.

Main medical station - emergency medical stations - temporary accommodation

The plan of the works shows the main and emergency medical stations and the temporary accommodation with their equipment and helicopter landing pads (Figure 8).

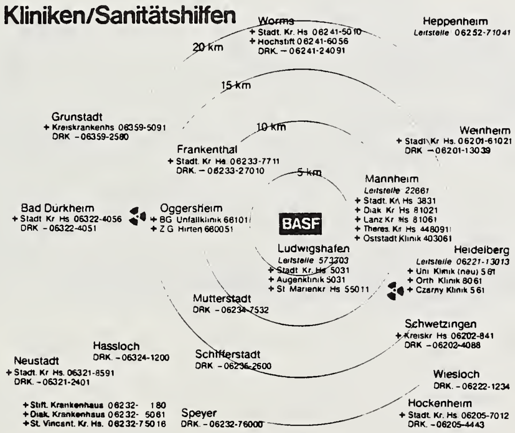


Figure 7

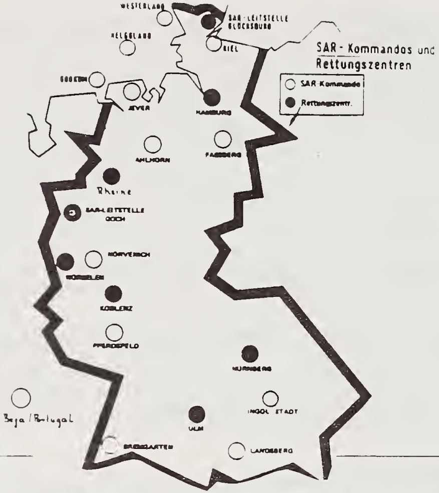


Figure 8

Medical supplies packed in sterile bags, 200 emergency beds, 400 blankets and 400 infusions are available for thousands of injured persons. Dressings, doctors' bags and stretchers can quickly be taken to the scene of the accident in two trailers.

The 7 ambulances, some of which are large-capacity, would probably not be able to cope in the event of a major emergency. In this case, immediate assistance from ambulance services outside the plant would be necessary.

Experience has shown that it is advisable in the event of a major emergency to contact local ministers of religion in good time so that church representatives are present to look after the seriously injured, if this is desired.

It should also be pointed out that measures to be taken in the event of accidents or disasters are observed and implemented not only in major plants of the BASF Group but also in medium-sized and small Group companies all over the world.

Dr. W. Arens and Dr. K. Kopp had prepared a paper entitled "Operations planning in hospitals in the event of major accidents". It was stated here that the custom of first attending to those seriously injured must be abandoned in the case of a major accident with many casualties, i.e. the matter-of-course individual treatment must give way to the claim of all the injured to attention. Surgical tactics, methods and organisation must always be adapted to the particular circumstances. A hospital naturally also has its disaster plan and will immediately be included in the alarm that is given in the event of a disaster. The roles of the doctor on duty and of the medical director in the implementation of all measures to be carried out are important: manning operations control, alerting doctors not on duty, deploying doctors for triage, preparing patients' discharge in order to release beds, organising operating procedures, exact documentation of all measures, summoning of ministers of religion for seriously injured, etc.

In the final paper given at the seminar and entitled "Possibilities of the Federal Defense Forces providing medical assistance in major emergencies in industry", M. Paul explained the technical and personnel assistance that the Federal Defense Forces can render. The search and rescue helicopters and their bases are available for emergencies at any time (Figure 9).

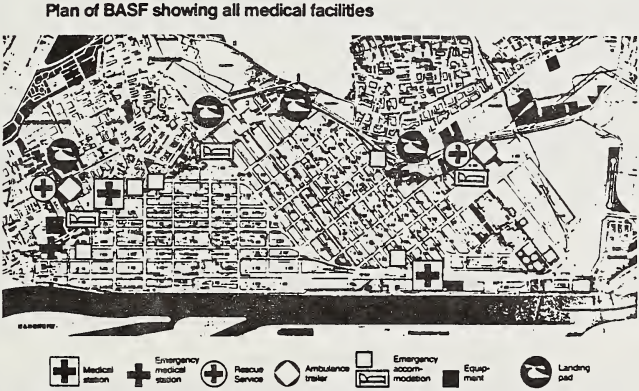


Figure 9: Search and Rescue Units and Rescue Centers

On request, special groups for treating shock, reanimation, anesthesia and emergency surgery can be used in the rescue operations and a main dressing station can be set up.

All papers that were given at the seminar were followed by detailed discussions in which particularly physicians in general practice took part and there was a general request for a practical exercise to test the theoretically discussed measures "in situ".

The practical emergency exercise took place on November 11, 1982. It was assumed that there had been a detonation and there were 50 injured who had to be rescued and given first aid.

The Fire Brigade, Medical Service, Safety Division, Security Force, Environment Department, Welfare Department, and Public Relations Department of BASF, press, radio, television, and the representatives of the municipal authorities, of the supervisory authorities, of the Employment Accident Insurance Funds and of the criminal investigation department all took part in the exercise. The municipal police had closed the appropriate streets in Ludwigshafen for the transport of the injured to hospital and informed the population about the exercise. The hospital alarm plan proceeded according to schedule and 50 beds were made available and the operating theatres were prepared. Specialist reprepresentatives of all the disciplines, and press, radio, and television representatives observed all the measures taken and in the concluding discussion minor mishaps were openly talked about in addition to a great deal of praise being voiced.

Summing up, it can be said that the seminar held on May 5 and the practical exercise carried out on November 11, 1982 in connection with "Precautions and measures for accidents in big chemical companies" proved their worth. As far as we know, it was the first time that a seminar and practical exercise had been held on this scale in the Federal Republic of Germany.

The lesson to be learned from this is that regular exercises reduce the risk of a disastrous error and make it easier to cope with a catastrophe.

Conclusions - Recommendations - International Cooperation

Safety as a duty of company policy

Cases of damage to health in chemical plants and various spectacular accidents which have occurred here and there around the world have given the public the impression that the chemical industry is a dangerous one, involving hazards which are difficult to calculate. This impression is incorrect. Safety is a basic precondition for the operation of chemical plants. This is particularly true of chemical factories with a production link-up. Progress in production technology has always meant progress in safety matters at the same time. We know that modern industrial society is increasingly concerned with safety, and this is as it should be. For the modern chemical industry, safety is not a static concept, but a permanent duty. Safety makes economic sense too, but above all, the safety of chemical plants is not merely the result of technological knowledge, it also results simply from a sense of responsibility. This responsibility is successfully practised on the basis of the special knowledge and specialized environment of the plants' own experts, within the framework of the regulations laid down by the legislatures in all countries. Independence, impartiality and objectivity are, for the expert personnel of a modern chemical concern, as fundamental to their responsible activity as they are to the experts employed by the legislatures.

Therefore, accident analysis in the modern chemical industry is equally important on the basic premise: every accident is avoidable, but if a disaster does happen, it is up to the safety engineer to establish the exact cause and circumstances, in the fullest detail. The primary purpose behind such accident investigations is not to attribute blame, but to analyse accurately the chain of cause and effect which led to the accident, and then to eliminate from this chain that link whose removal offers the best assurance that the accident will not happen again.

It is, therefore, important that the modern chemical industry seeks institutionalized cooperation in disaster control planning based on expertise and experience, with all the organs responsible for the protection of safety. Here the industrial physician can play an important role. Cooperation, however, also after a disaster, requires a constant worldwide dialogue. The physician in the chemical industry must be informed when, where and what kind of a disaster has happened in the world. It is important to learn from accidents, to pass on the lessons learned by publishing them in scientific papers, and to counteract human error by fundamental training, constant instruction, intensive training in the correct course of action from a safety point of view, effective technological measures, unambiguous organisation of the working cycles and clear responsibility.

Physicians in the chemical industry not only have a duty to do everything for the employees' safety and protection, they are also responsible for ensuring that they are not alarmed by uninformed statements concerning safety in this industry.

National laws, ordinances, recommendations and accident prevention regulations are necessary. However, not every industrial activity should be regulated. Personal responsibility, also in disaster control planning, is more effective than regulations.

Safety guidelines, like those issued by the Board of Executive Directors of BASF for the Group companies throughout the world, are the best guarantees for preventing a disaster and protecting the employees. Occupational safety in our company (as in many others) is a special obligation, and productivity and profitability must be subordinated to safety.

The Journal of Commerce, New York, of December 30, 1981, states under the headline: "Chemical Sector - Safest US Industry" that according to the National Safety Council's list of safest U.S. industries in 1981 "the chemical industry now ranks first among 43 basic U.S. industries in the lowest number of incidents of occupational illness and injury involving days away from work and deaths."

Successful disaster control planning can only be carried out in a matter-of-fact atmosphere and with factual arguments. Polemic, no matter who uses it, neither furthers the cause nor does it do justice to the seriousness of the subject.

By virtue of his ethical principles, no doctor can or will evade his responsibility to save and maintain life. Particularly we doctors in the chemical industry must cooperate in taking measures to ensure that as many people as possible are helped effectively under very adverse conditions after there has been a disaster.

Training in first aid is therefore absolutely essential at the university and later during futher training.

It should be added that, following a major disaster, national resources may not be sufficient to meet relief needs, and assistance from the international community will, therefore, be required. This assistance may then be given by appropriate specialised agencies of the United Nations. Since 1972, the Office of the United Nations Co-ordinator for Disaster Relief (UNDRO) has been responsible for ensuring speediest response to needs after a very severe disaster.

What I consider to be the most important factor in our efforts to carry out "risk assessment and intervention in disaster control planning", is the encouraging fact of our successful and friendly international cooperation in the comprehensive field of safety protection in the chemical industry. Our generation has been faced with a lot of new challenges; Medichem started to cooperate across frontiers more than ten years ago in discussing all serious subjects and topics of our daily work, and we have learned a lot from each other. Only if we can continue to tackle the tasks still before us on a broad international basis, shall we achieve further success in maintaining the safety and health of those in our care, which is what we are all striving for. Each of us is called upon to play his part. Let me close with a quotation from the ILO Encyclopaedia, given at the end of the chapter "Disaster". "A disaster can, in fact, provide the impetus not merely to rebuild the old, but to build in such a way as to provide a better life for those who survived, and a worthy memorial for those who did not ..."

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ACUTE RESPIRATORY REACTIONS TO CHEMICAL EXPOSURES: FOCUS ON OXIDES OF NITROGEN

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Introduction

On February 15th of this year, I was on call for the respiratory services of the Royal Victoria Hospital in Montreal. An urgent request was received to take in transfer a 35 year old man whose respiratory status was deteriorating rapidly; on 100% O_2 delivered via a volume cycled ventilator he was hypoxemic (PO_2 30 mm) with a mixed respiratory and metabolic acidosis (p CO_2 48 mm, pH 7.25). The physician in charge believed high frequency ventilation which we could offer might save his life. He died on arrival at our hospital. The parents of the patient who accompanied him to our hospital told us that their son had been employed for approximately 18 months in an explosives plant, and that on the evening before he was admitted to the local hospital an accident had occurred at work which involved the spillage of acid requiring cleanup. Six hours later he was admitted to the local hospital with abdominal discomfort; 10 hours later his breathing became laboured; 24 hours later he died. Following the coroner's inquest, a judicial enquiry was set up to investigate the circumstances of the accident (1). When the report is released, it will be possible to supplement the history of this patient with a more precise description of his occupational exposure at the accident which led to his death.

Last year, I was a visiting professor to the chest disease service at Dalhousie University, NS; the first case presentation on which I was asked to comment concerned a man admitted with acute pulmonary edema following an explosion in a Cape Breton pulp and paper plant. According to news reports, an explosion which occurred in a tank of nitric acid, released a cloud of yellow smoke, blew out a wall and shot a 10 ton heat exchanger 17 metres across a yard. Two men were killed immediately, 10 were hospitalized, 3 died the next day. The case I saw survived. He was one of two cases evacuated to Halifax by ambulance. The condition of the second man had deteriorated so rapidly en route that he had been admitted to a regional hospital where despite all efforts to resuscitate he had died.

Several years ago, three men were admitted to the Royal Victoria Hospital in Montreal with a medical history of delayed onset of symptoms similar to that of the first patient. All were welders; all had spent a full shift with overtime inside a ship's boiler to free a propeller shaft. All developed pulmonary edema; all survived. Before coming to Canada, I worked in Johannesburg where we studied 7 men, all of whom had been exposed to underground blasting accidents, all of whom had suffered pulmonary edema of varying degrees of severity. All these men had survived, some with residual lung damage (2).

Why, you may ask, should a recital of one chest physician's clinical experience introduce this presentation on acute chemical respiratory injuries? For several reasons: i) deaths from acute chemical pulmonary edema can only be classified as disasters: the topic is disaster control; ii) my experience and that of our hospital is undoubtedly duplicated not only across Canada but also in other industrialized countries. Fatal cases occur, not ofter, not usually in the same plant, not usually referred to the same medical service. Thus, experience is not concentrated: accidents catch out the plant personnel and engineers, plant medical services as well as the hospitals providing the emergency coverage. iii) at potential risk in Canada are a large number of men and women employed in a variety of industries and doing a variety of jobs; the same must be true in the many countries represented here today. iv) this audience in particular gathers individuals who are uniquely placed to devise effective control strategies to avoid these accidents, as well as to catalyse documentation on treatment and foster research on basic mechanisms of acute chemical lung injury and their treatment.

The oxides of nitrogen

The gases responsible for this type of chemical lung injury producing delayed onset acute pulmonary edema are the oxides of nitrogen (3). Of these, nitrous oxide (NO_2) is the most prevalent in the atmosphere and is generated from anaerobic processes in the soil and surface layers of the ocean (.25 ppm). NO and NO_2 are the most abundant in urban areas being derived from high temperature combustion processes. In equilibrium, the oxidation rate of NO at room temperature is proportional to its concentration: 90% is reached in 3.6 minutes at 10,000 ppm, in 36 minutes at 100 ppm, in 6 hours at 1 ppm. N_2O_3 occurs in negligible amounts in equilibrium status. Whereas NO is colourless, odourless, NO_2 is brown-orange when pure (100%), orange at 20% dilution, yellow at 5% dilution and colourless at 0.1% (i.e. 100 ppm).

Acute pulmonary edema

The pathological appearances of acute chemical pulmonary edema tell their own story: one does not need to ask why the outcome may be so disastrous. Characteristic features of the fatal case on gross pathological examination are edema and congestion of the larynx, trachea and lungs, and on histologic examination severe peribronchiolar, interstitial and airspace edema with hyaline membrane formation (4). In the first case I described it was estimated that less than 10% of alveoli were patent for gas exchange. The clinical features are also well exemplified by this case. They have been on medical record for almost 180 years; the first report appeared in 1804 in Le Journal de Medicine, Chirurgie et Pharmacie and described two cases, a Lyon merchant, and his watchdog (5). Characteristic is the delay in the appearance of the respiratory symptoms (at times up to 48 hours), and death due to failure of oxygen exchange.

Medical management is directed at maintenance of oxygen exchange to sustain life until the edema has subsided (6-9). This is of course a matter for a specialized center, and the treatment modalities include all those available for use in management of the adult respiratory distress syndrome due to other causes. The issue of whether effective treatment can be offered in the latent period is under debate; several measures are advocated. The first is the administration of corticosteroids; in our hospital it has been the practice to administer steroids for at least 48 hours in those thought to be at risk, assessed on the basis of changes in PO_2, alveolar-arterial O_2 differences and/or the presence of basal rales. In passing it should be noted that steroids are also used when the edema is florid. Because this practice was recently questioned, we reviewed recommendations in standard texts and published reports and there appears to be a consensus in favor of this treatment when the injury is due to exposure to the oxides of nitrogen (6-9). Other aspects of treatment are emphasized in a document on "La Securité et l'hygiène du travail dans l'industrie des substances explosives" published in France; these include the need for immobilisation (bed rest) for 48 hours following exposure, as well as inhalation for 20 minutes of a solution of ammonia 2.0 gm/l nebulised by an oxygen flow at 9l/m (1,p339). The latter is not described in North American texts.

Sub-acute and chronic lung injury

There are almost certainly residual effects in some individuals who survive the acute episode; others appear to recover completely. We had the opportunity to study a young colleague of the first case I described, working at the same plant, who had been the victim of work accident which occurred the day after the fatal exposure of his mate, but with a more fortunate outcome. One month after the accident the chest radiograph and lung mechanics were within normal limits. However, there was a deficit in vital capacity, and though exercise performance tests were normal insofar as ventilation, heart rate and gas exchange were concerned, the maximum level achieved was less than expected. Whether this was the consequence of his accident is a matter of speculation. If so, it may have been due to bronchiolitis obliterams of mild degree, a recognized late complication of acute exposure. This proliferative disease in small airways, if progressive and if extensive enough may be fatal. Adequate treatment with steroids at the time of the acute exposure is thought to prevent this complication, and the reports of such cases in the literature antedate their widespread use of steroids in the treatment of acute chemical edema.

Residual chronic effects have also been described by ourselves in goldminers exposed to underground blast accidents and others hold the same view. For instance, Kennedy reviewed the files of 100 British coalminers (10) following introduction of a new type of hydrox shell for blasting in a North England coal field; 4 men with acute pulmonary edema and several with severe dyspneoa diagnosed as bronchitis and emphysema which he attributed to exposure to the oxides of nitrogen underground. Levels recorded in these mines ranged from 0.8 - 4.5 ppm on the coal face where ventilation was good.

High level human exposures

At risk for accidental high exposure are workers engaged i) in the manufacture of nitric acid; ii) in industries involving processes which use or make products containing nitric acid; iii) in operations which involve use of nitrocellulose in blasting particularly in enclosed spaces eg. underground mining; iv) in handling silage material (the anaerobic processes which occur 24 to 48 hours following the ensilage of green plant material release of the oxides of nitrogen; v) in operations where combustion takes place in enclosed spaces eg. welding, fire-fighting, particularly if the combustible materials contain nitrogen (eg. the Cleveland Clinic fire in which nitrate coated x-ray films in storage caught alight, the Coconut Grove night-club fire in Boston in which the fire caught the cellulose plastic decorative coverings of walls). In 1978, the Science Council of Canada estimated that there were 13 plants involved in the manufacture and use of nitric acid in Ontario, 11 in Quebec, 10 in Alberta and one each in Manitoba and British Columbia. No estimate was provided of the number of men and women at risk.

Freak accidents may also occur, for instance a series of anaesthetic deaths due to N_2O tanks contaminated by NO_2 during filling (3). One of the best documented occurred in a Titan Missile Silo near Wichita, Kansas (11) reported in 1980. An accident resulted in 48,200 litres of liquid nitrogen tetroxide spilling into the silo complex, and vaporisation led to its general dispersal. There were 24 personnel on duty at the time; of 3 who had heavy exposure, 2 died and one had prolonged hospital treatment without complete recovery. The other 21 had light exposure; 6 experienced transient symptoms including cough, chest tightness, shortness of breath. (estimated exposure 10 minutes only); 4 had delayed hypoxemia 2 weeks later and received steroids; a further 6 developed headaches within 2 weeks after exposure (3 of whom showed normal after extensive neurologic examination). One year later, 4 out of 6 remained adversely affected by the neurological symptoms. The report contains no information on exposure levels: it was assumed however that because nitrogen tetroxide volatises readily giving off NO_2 until equilibrium is reached, the latter gas was the major contaminant.

Exposure Response Relationships

A WHO Report (12) states that exposure to 300-500 ppm (5-10 seconds) is fatal and pulmonary reactions occur after exposure 25-77 ppm (after 30 minutes). Levels of 88-167 ppm have been recorded following explosions. Tobacco smoke contains levels from 500-940 ppm, while levels between 1 and 21 ppm have been recorded around gas cooking stoves.

Long-term low level exposure and its effects on human health

Acute respiratory reactions in the form of chest illnesses diagnosed as bronchitis, chest colds and/or wheezing may occur at much lower levels of exposure to the oxides of nitrogen such as are found in community air pollution. The evidence comes primarily from comparing rates for respiratory illness in children living in areas with different levels of environmental pollution due to the oxides of nitrogen, the main sources being automobile exhaust and industrial activity, aided by the action of sunlight (13-17).

One of the earlier studies, in Chattanooga, Tennessee, was carried out in response to community concern over rising levels of NO_2 pollution recorded after the opening of a munitions plant (13); is this deleterious to the health of children? asked the citizens. Findings were a significant increase in bronchitis morbidity in school children living in the areas of higher pollution compared to those living in the areas of lower pollution for the second and third year following the opening of the plant and in infants in the third year after its opening.

In the UK evidence comes from a series of studies carried out as part of a larger research program investigating health and growth in primary school children started in 1972 in 34 regions of the country. Excesses of cough, bronchitis, wheezing and chest colds were recorded in homes using gas ranges compared to electric ranges (14) and direct measurements revealed differences in NO_2 levels in the order of 10 fold, 112 ppb compared to 19 ppb in a sample of the homes (15). Similar findings were subsequently reported from Boston (16, 17). In addition animal studies suggest an increased susceptibility to infections with low level exposure, as well as evidence that such exposures lead to emphysema (8).

The reason for raising the issue in the present context is two-fold: first, to complement the information on high-level short-term exposure (if the latter occurs in industrial setting, the potential for low level long-term exposure must also exist); and second, if there is an increase in acute respiratory illnesses in children with low level long-term exposure, does this risk pertain to adults with exposures in the industrial setting? (a question susceptible to clinical study).

Conclusions

In conclusion, two issues merit re-emphasis, the first related to what is known about the health hazards of exposure to the fumes of the oxides of nitrogen, the second to what is not known. Both issues are of particular relevance to those charged with health protection in the chemical industry.

First, the clinical features of high level exposure have been on record for almost 180 years including the documentation of the treacherous delay of up to 48 hours between exposure and the onset of respiratory distress. Moreover there is a certain clinical consensus on the usefulness of steroid therapy in the immediate post-exposure period. Nevertheless, fatal industrial accidents continue to occur because these two items of information are not applied to accident management. The reason is not hard to discern: such events are infrequent, and given the often high turnover rates in industry workers, shop stewards and managements are invariably not on the alert to deal with the event. The same appears to be true of some plant medical services and of some acute care referral services: physicians today continue to make the same mistake as was made by the physician of the Lyon merchant in 1804, pronounce the patient out of danger 12 hours and be obliged to pronounce him dead after 24 hours. How can we be sure that all concerned are correctly informed? This audience is uniquely placed to ensure that this happens. A corollary to this is that accidents of this sort are clearly engineering failures, and hence preventable.

Second, on the issue of absence of knowledge, two areas should be addressed. The first relates to the therapy of acute nitrogen-dioxide induced pulmonary edema; animal models could certainly be used to assess the value of steroid therapy in the period between exposure and the onset of pulmonary damage, thereby strengthening (or not) the clinical consensus in favor of early administration. The second relates to documentation of what health effects, if any, are detectable in adults with long-term low level exposure; epidemiologic studies of exposed workforces could provide such answers. A supplementary issue relates to whether such exposures predispose adults to respiratory illness. Both these issues have been recently identified by the Health Effects Institute of Boston as important research questions, and they also merit the serious attention of MEDICHEM.

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L'APPORT D'UN LABORATOIRE D'HYGIENE INDUSTRIELLE AUX MEDECINS DU TRAVAIL LORS D'UN ACCIDENT D'ORIGINE CHIMIQUE

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Abstract

As an occupational health laboratory established at Tricastin, a large industrial complex working on the chemical and physicochemical processes of uranium enrichment, we have a great deal of experience with accidents. For more than 20 years, we have been one of the agencies which intervenes in small or large scale accidents, to provide the occupational physician and the engineers responsible for protection with the results of contamination on biologic samples or the environment. In our industrial complex, the major chemical product is uranium hexafluoride (UF_6), which immediately breaks down in humidity into HF and uranium oxyflouride ($U0_2F_2$). In addition to immediate medical aid necessitated by the acute toxicity of fluorohydric acid, it is necessary to very quickly know the degree of contamination of the workers in order to evaluate the risk of acute nephritis from Uranium which in an accident is considered to be a heavy metal.

Our organization is well set up consisting of: teams of specialized technicians, teams on duty outside of normal working hours, and material and selected techniques for emergency examination. Within two hours we can provide the occupational physicians with results which allow them to select from among the workers exposed in the accident the ones who were most exposed and, if necessary, to observe these workers.

In other respects, we frequently intervene, at the request of official organizations or heads of industrial firms or occupational physicians, in accidents involving organic or mineral poisons. But our efficiency is hampered by a limited knowledge of the local industrial conditions; each case becomes a specific case and time must be taken to learn the circumstances of the accident, the products used, their toxicity, etc.

Our experience can serve as an example to the chemical industry where accidents are frequent.

National authorities should be made well aware of the advantages of developing laboratories specializing in industrial health which are designed to be able to intervene in accidents, therefore mandated to have beforehand, a good knowledge of the conditions in which they occur.

Résumé

Laboratoire d'Hygiène Industrielle, implanté dans le Tricastin, complexe industriel important où l'on met en oeuvre des procédées chimiques et physico-chimiques d'enrichissement de l'Uranium. Nous avons une très grande expérience des situations accidentelles. Depuis plus de 20 ans, nous sommes un des organismes qui intervient, lors d'accidents mineurs ou de grande ampleur, pour fournir aux médecins du travail et aux ingénieurs chargés de la protection les résultats de contamination sur des prélèvements biologiques ou de l'environnement. Sur notre complexe industriel, le produit chimique majeur est l'hexafluorure d'Uranium (UF_6) qui se décompose immédiatement en présence d'humidité en HF et oxyfluorure d'Uranium (UO_2F_2). Au delà des gestes immédiats de soins médicaux nécessités par la toxicité aigüe de l'acide fluorhydrique, il est indispensable de connaître très rapidement le degré de contamination des travailleurs pour évaluer le risque de néphrite aigue à l'Uranium considéré en situation accidentelle comme un métal lourd.

Notre organisation est bien rodée: équipes de techniciens spécialisés, disponibilité en dehors des heures normales de travail, matériel et techniques sélectionnés pour les examens d'urgence. En deux heures nous pouvons fournir aux médecins du travail des résultats qui leur permettent de faire un tri parmi les travailleurs exposés lors de l'accident et de mettre en observation, si cela s'avère nécessaire, les plus exposés.

Par ailleurs, nous intervenons fréquemment, à la demande d'organismes officiels, ou de directeurs d'entreprises industrielles ou de médecins du travail, dans des situations accidentelles dues à des toxiques organiques ou minéraux. Mais notre efficacité est entravée par une moins bonne connaissance des conditions industrielles locales; chaque cas devient un cas particulier et il faut prendre le temps d'investiguer les circonstances de l'accident, les produits utilisés, leur toxicité, etc. Notre expérience peut servir d'exemple à l'Industrie chimique où des situations accidentelles sont fréquentes.

Il nous apparait nécessaire d'attirer l'attention des autorités nationales sur l'intérêt qu'il y aurait à mettre en place des laboratoires spécialisés en hygiène industrielle ayant la vocation d'intervenir dans des situations accidentelles, donc ayant reçu mission de connaître au préalable leurs conditions d'opération.

Laboratoire d'Hygiène Industrielle implanté en France sur le Tricastin, complexe industriel de 6 établissements différents et de nombreuses entreprises d'assistance technique où sont mis en oeuvre dans le domaine nucléaire et para nucléaire des procédés chimiques et physico-chimiques d'enrichissement de l'Uranium, de traitement de surface, de chimie du Fluor, de production d'énergie électrique, de fabrication d'éléments combustibles pour les centrales nucléaires, etc. Nous avons une très grande expérience des situations dites accidentelles.

Expérience acquise

Dans le tricastin

Depuis plus de 20 ans, nous sommes un des organismes qui intervient, lors d'accidents mineurs ou de grande ampleur, pour fournir aux médecins du travail et aux ingénieurs chargés de la protection, les résultats de contamination sur des prélèvements biologiques ou de l'environnement. Dans notre complexe industriel, le produit chimique majeur est l'Hexafluorure d'Uranium (UF_6) qui se décompose immédiatement en présence d'humidité en HF et oxyfluorure d'Uranium (UO_2F_2) selon la réaction suivante:

$$UF_6 + 2H_2O \rightarrow UO_2F_2 + {}_4\ HF$$

L'inhalation d'UF_6 provoque deux types de manifestations:

- effets immédiats: atteinte chimique des voies respiratoires due à la libération de l'acide fluorhydrique, avec suffocation, douleurs rétrosternales et risques d'oedème aigu du poumon;

- effets retardés: altérations rénales provoquées par l'uranium si la quantité inhalée était suffisante, avec anurie, albuminurie, cylindrurie, urémie, etc.

Au delà des gestes immédiats de soins médicaux nécessités par la toxicité aigüe de l'acide fluorhydrique, il est indispensable de connaître très rapidement le degré de contamination des travailleurs pour évaluer le risque potentiel de néphrite aigüe due à l'Uranium considéré en situation accidentelle comme un métal lourd.

Notre organisation est bien rodée: équipes de techniciens spécialisés, disponible en dehors des heures normales de travail, matériel et techniques sélectionnés pour les examens d'urgence. En deux heures nous pouvons fournir aux médecins du travail des résultats qui leur permettent de faire un tri parmi les travailleurs exposés lors de l'accident et de mettre en observation, si cela s'avère nécessaire, les plus exposés.

Lors de ces incidents les effectifs concernés varient de quelques personnes à quelquefois plusieurs centaines de personnes. Nous pouvons citer 2 exemples:

Ainsi en 1965, lors du'un incident survenu dans l'usine pilote du centre CEA de Pierrelatte, nous effectuâmes de très nombreux contrôles. Cet indident n'a eu heureusement aucune conséquence fâcheuse pour le personnel. Celui-ci était alors en service de jour, et bien qu'il n'y ait pas eu d'agents sérieusement atteints, il a été décidé, afin de parfaire nos connaissances dans le domaine de la protection, de contrôler un nombre très large de personnes. Cette méthode avait en outre l'avantage d'éviter qu'il y eût par hasard un individu non contrôlé et susceptible à l'extrême limite d'avoir été intoxiqué.

Schématiquement quatre catégories d'individus furent contrôlées:

a) Personnel directement exposé

115 personnes étaient susceptibles d'avoir inhalé accidentellement à 16 h de l'UF_6. Pour cette catégorie, il fut possible d'effectuer un prélèvement des urines immédiatement après l'inhalation (17 h) en vue d'établir un diagnostic et un pronostic de la contamination individuelle, et d'apprecier rapidement l'importance de l'incident. Un flacon pour recueillir les urines des 24 heures leur fut remis dans le but ultérieur d'évaluer la contamination individuelle.

Des examens de selles et de sang furent pratiqués pour certains de ces individus. L'excrétion urinaire d'une personne fut suivie durant 22 jours.

b) Personnel indirectement exposé

Le 2° et le 3° jours suivant l'incident, 323 personnes qui n'étaient pas présentes sur les lieux mêmes, mais qui auraient pu être contaminées, effectuèrent le prélèvement d'un échantillon d'urines pour contrôle.

c) Visiteurs et personnel ayant effectué la décontamination des locaux

Le risque de contamination interne de 358 personnes entrant dans le local considéré, ou effectuant sa décontamination, fut apprécié en exigeant des prélèvements d'urines à la fin de la journée de travail.

d) Personnel ayant effectué la décontamination du matériel contaminé

Pendant une période de 42 jours, 38 personnes chargées de la décontamination du matériel proprement dit effectuèrent un prélèvement d'urine journalier.

Les nombreux contrôles opérés sur ce nombre relativement élevé d'agents ont permis l'établissement de statistiques intéressantes sur l'élimination de l'uranium inhalé par certaines personnes à des doses légères.

En 1977, un incident du même genre s'est produit sur le complexe industriel du Tricastin, dû à la libération accidentelle d'une grande quantité d'UF_6; il a concerné plus de 400 personnes fureut exposés. Nous avons, comme pour celui de 1965, pratiqué un très grand nombre de contrôles.

En dehors du tricastin

Par ailleurs, nous intervenons fréquemment, à la demande d'organismes officiels, ou de directeurs d'entreprises industrielles ou de médecins du travail, dans des situations accidentelles dues à des toxiques organiques ou minéraux. Mais notre efficacité est entravée par une moins bonne connaissance des conditions industrielles locales; chaque cas devient un cas particulier et il faut prendre le temps d'appréhender les circonstances de l'accident, les produits utilisés, leur toxicité, etc.

TABLEAU 1: Bilan Général Des Contrôles Effectués

	Nombre de personnes contrôlées	Nombre d'examens effectués sur			
		Les urines		Selles des 72h	Sang
		suivant immédiatement l'inhalation	jours suivant l'inhalation		
Personnel directement exposé	115	109	395	7	11
Personnel indirectement exposé	323	–	361	–	–
Visiteurs et décontamineurs du local	358	–	1463	–	–
Décontamineurs du local	38	–	326	–	–

Les nombreux contrôles opérés sur ce nombre relativement élevé d'agents ont permis l'établissement de statistiques intéressantes sur l'élimination de l'uranium inhalé par certaines personnes à des doses légères.

Nous pouvons citer quelques exemples vécus au cours de notre activité quotidienne:

- Dans une entreprise de mécanique, les ourvriers ressentaient des malaises lors de leur travail de dégraissage de pièces métalliques. Les contrôles toxicolgiques, effectués sur les urines de travailleurs chargés des opérations de dégraissage devant des cuves parfaitement conçues (trichloréthylène), étaient nettement positifs (supérieurs au maximum permissible TCA + TCE). Par contre les contrôles d'ambiance pratiqués lors de la marche normale de ces installations étaient toujours normaux et bien inférieurs à la valeur limite recommandée par les Hygiénistes Américains. En réalité une enquête révéla que les ouvriers inhalaient des vapeurs d'un solvant chloré en assez grande quantité lors des opérations de nettoyage des cuves de dégraissage dans lesquelles il existait des boues très fortement chargées en solvant.

- Dans une entreprise de fabrication de matières plastiques (résines époxy et résines polyuréthanes), nous avons conseillé au Médecin du Travail des recherches de MOCA (Méthylène bis Ortho ChloroAniline) dans les urines pour connaître l'origine des brûlures aux mains de certains ouvriers. Ces contrôles s'avérant positifs permirent d'améliorer les conditions de travail.

- Nous eûmes à analyser le sang et les urines de deux ouvriers décédés au cours de leur travail dans une cuve. Les analyses de sang pratiquées par la technique de "head space" en chromatographie en phase gazeuse ainsi que les analyses d'urines révélèrent la présence en grande quantité d'hydrocarbures benzéniques et de métobolites.

- Lors d'ingestions accidentelles de pesticides organophosphorés, nous avons été amenés à effectuer des recherches et dosages des toxiques et de leurs métabolites (dialkylphosphates) dans les urines, le liquide de lavage gastrique et les cholinestérases globulaires dans le sang.

- Les exemples de l'expérience acquise en pratique quotidienne pourraient être énumérés en très grand nombre; on peut encore citer des accidents avec l'Arsenic, le chrome des composés benzéniques, etc.

- Mais pour terminer sur un exemple qui montre bien la complexité des situations vécues, nous décrirons une situation accidentelle survenue dans une usine de confection de vêtements de ski. Il s'agissait d'une moyenne entreprise (230 personnes) implantée dans le centre de la France dans une zone industrielle (usine de galvanoplastie, entreprise de peintures et de revêtements époxy), bordée par une autoroute et une rivière servant d'égouts pour les entreprises industrielles situées en amont. Des incidents se produisaient parmi les travailleurs (population en majorité féminine) provoquant des malaises suffisamment importants pour justifier l'hospitalisation des sujets par l'intermédiaire du SAMU local. Ces incidents se produisaient en septembre et décembre dans des conditions météorologiques précises: le lendemain d'un orage ou d'une pluie violente par temps couvert, précédés d'odeurs très fortes (odeurs d'égouts, d'oeufs pourris, etc.) Les symptomes observés étaient les suivants:

- Maux de tête violents une heure et demie après le début du travail, accompagnés de gêne respiratoire, d'étouffements, de nausées pouvant aller jusqu'à une perte de connaissance, pour certains langue blanche et pâteuse - gorge sèche - teint jaune - faiblesse musclulaire - état de somnolence - crampes musculaires - irritabilité - fatigue générale - trouble de la mémoire - trouble de l'équilibre - irritation oculaire - éruption cutanée - démangeaisons.

Les différents organismes officiels de la région s'étaient préoccupés de cette situation: Direction de l'Action Sanitaire et Sociale, Service de Mines, Médecine du Travail (Université), Centres Hospitaliers, Commissariat de Police, etc., sans pouvoir déterminer l'origine et les causes de ces malaises. En désespoir, la Direction de l'entreprise fit appel à notre Laboratoire. Nous effectuâmes une enquête, en dehors des périodes d'accidents, dans l'entreprise elle-même, le voisinage industriel et la région. Nous fûmes amenés à envisager 5 hypothèses sur l'origine de ces malaises:

- le travail lui-même ou les produits intervenant dans la production, mais aucune circonstance de la production ou produit chimique ne pouvait justifier la situation observée.

- un acte de malveillance de la part d'un(e) employé(e) de l'entreprise cette hypothèse fut écartée après une enquête de police approfondie et des analyses d'atmosphère pratiquées dans notre laboratoire.

- une origine psycho-somatique fut évoquée, en raison de la très forte proportion de personnel féminin; sans pouvoir être totalement écartée, elle ne fut pas retenue comme cause déclenchante mais admise comme facteur aggravant.

- la pollution chimique créée par l'usine de Galvanoplastie avoisinante fut mesurée par notre laboratoire. On pût ainsi constater que les malaises observés ne pouvaient pas être rapportés à ce voisinage malgré l'avis pour le mois subjectif de l'entreprise de confection.

- enfin, la 5° et dernière hypothèse, l'Hydrogène Sulfuré en raison de la coexistence de plusieurs facteurs allant dans un même sens (malaises, chronologie des incidents, odeurs, circuit d'évacuation des eaux usées, etc.). Notre travail consista alors à démontrer la véracité de notre hypothèse. Pour cela nous opérâmes en 2 phases distinctes:

a) mise en évidence d'un mauvais fonctionnement des réseaux d'eaux pluviales et eaux usées avec possibilité d'interconnexion entre les deux d'une part, et mauvais réglage des circuits de ventilation et d'aération d'autre part créant ainsi les conditions permettant l'accumulation en certains points des polluants ayant une origine extérieure à l'entreprise.

Pour cela nous utilisâmes notre technique au gaz traceur, le SF_6 (hexafluorure de Soufre). If s'agit d'un gaz incolore, inodore et non toxique qui, lorsqu'il est libéré en un lieu (atmosphère, canalisation, etc...), suit les mouvements des masses d'air donc les transferts de toxiques d'un point à un autre. Nous savons le mesurer sur le terrain en continu et en instantané grâce à nos appareils portatifs de chromatographie en phase gaxeuse.

b) mise en évidence de la présence d'Hydrogène Sulfuré par un appareil de mesure en continu qui révéla ainsi des périods où l'on observait des bouffées importantes de ce gaz.

Ainsi nous pûmes démontrer à la Direction de l'entreprise, les partenaires Sociaux et les Adminsitrations régionales concernées, l'origine et la cause des malaises observés parmi le personnel. Cet hydrogène sulfuré était crée par fermentation de matières organiques dans les conditions particulières d'installation de l'entreprise:

- certaines prescriptions du règlement sanitaire départemental concernant les eaux vannes donc les fosses septiques n'avaient pas été respectées,

- des remontées d'eaux vannes en provenance des fosses septiques s'étaient produites dans les ateliers,

- lors des incidents, des remontées d'odeurs par les fosses septiques des usines avoisinantes avaient été constatées,

- la rivière bordant l'usine est un véritable égout: les eaux domestiques et les eaux industrielles se déversent directement dans la rivière. Certains rejets ne subissaient aucun prétraitement de détoxication destiné à réduire la charge polluante. Elle dispose d'un écoulement torrentiel: des variations brutales de débit de 1 m^3 s^{-1} à 99, m^3 s^{-1} peuvent se produirent très rapidement,

- la nappe phréatique est à une profondeur de 2 à 3 mètres,
- le terrain sur lequel est implanté cette usine bien qu'assaini est marécageux,
- la digue de la rivière, détruite au moment de l'agrandissement de l'usine, pour assainir le terrain, n'a pas été reconstruite,
- les réseaux d'eaux vannes et d'eaux de ruissellement sont géographiquement très proches. Il existe même une liaison entre le réseau d'eaux vannes et le réseau d'eaux pluviales après la fosse septique de l'usine,
- les ateliers sont en atmosphère étanche et confinée. Le système de chauffage est asservi à la température régnant dans les ateliers.

Recommandations

Notre expérience en ce domaine nous permet de proposer un certain nombre de recommandations pour pouvoir traiter des situations accidentelles dans les meilleures conditions.

Avant l'accident

- On doit considérer que l'éventualité d'un accident doit être envisagée pour toute installation industrielle afin d'avoir prévu les secours.
- Il est indispensable que le Médecin du Travail connaisse bien les conditions de travail de son personnel: produits manipulés, adjuvants, réactions d'incompatibilité entre les produits pouvant créer les conditions d'une réaction dangereuse. Il peut obtenir ces renseignements auprès de la Direction de la Production et de l'Ingénieur de Sécurité. Dans les petites entreprises, il peut faire appel à un Laboratoire d'Hygiène Industrielle qui lui apportera son assistance pour établir ce constat.
- A ce stade de préparation en vue d'un éventual accident, il nous parait important de mentionner les études de prévention que nous réalisons couramment à la demande des entreprises, grâce à notre expérience acquise dans le domaine nucléaire, ce sont:

* Etude des risques liés au procédé employé ou à l'installation; (identification des produits employés ou stockés, des cheminements des produits et des conditions de manipulation dans l'entreprise)

* Etude des risques entraînés par une défaillance matérielle;

- Etude des risques entraînés par une erreur humaine;

- Prévention des conséquences d'un incident ou d'un accident.

En outre, nous réalisons, grâce à notre technique au gaz traceur SF6, des études d'installations industrielles qui nous permettent de fournir aux responsables des renseignements essentiels à une bonne prévention des accidents:

- établissement d'une cartographie du transfert des polluants à l'intérieur de bâtiments en fonction des entrées d'air (naturelles et mécaniques) et de la convection thermique. Les lâchers de SF6 se font alors au niveau des sources de polluants.

- détermination des concentrations en produits toxiques au niveau de différents postes (dans la mesure où l'emplacement et le débit des sources sont connus).

- amélioration de l'efficacité de hottes, sorbonnes où sont manipulés des produits toxiques (mesures de la concentration en SF6 dans la gaine d'extraction).

- recherche de la contribution polluante de différentes sources à l'insalubrité d'un poste de travail.

- optimisation de l'emplacement d'appareils déclenchant une alarme en cas de fuites accidentelles de gaz toxiques (étude basée sur la mesure du temps de transfert du traceur aux points sensibles).

- mis en évidence de l'existence et de la part de recyclage d'air extrait par les gaines de soufflage de l'air extérieur.

- recherche de l'étanchéité d'enceintes de confinement: localisation, mesures des taux de fuites.

Enfin, nous pouvons concevoir un système de surveillance permettant une bonne prévention des accidents:

- choix d'un système de détection d'incendie approprié (détecteurs de fumée, infrarouge, thermovélocimètre),

- choix d'un système d'explosimètre le cas échéant, selon la nature du gaz mis en jeu et des risques d'interférences,

- définition de la structure minimale à donner à un système de surveillance pour prendre en compte tous les risques encourus (alarme seule répercutée sur un poste de contrôle, ou mise en oeuvre d'un système automatique).

Un accident créant toujours un état de panique, il est nécessaire que le médecin du travail dispose au niveau de l'entreprise de locaux adaptés à la réception, au tri et aux premiers soins pour le personnel impliqué dans l'accident.

Il faut aussi qu'il ait établi un accord formalisé avec un Laboratoire d'Hygiène Industrielle compétent, disposant d'un matériel de mesures toujours opérationnel, c'est à dire en constant état de marche, et de techniciens de laboratoire expérimentés doués d'un grand sang-froid.

Cet accord formalisé à l'avantage de permettre au Laboratoire d'Hygiène Industrielle contractuel de se préparer à ce qui lui sera demandé par le médecine du travail lors de l'accident:

- nature des examens à effectuer
- appareils de laboratoire en état de fonctionnement
- véhicules pour se rendre sur les lieux de l'accident si nécessaire
- techniciens de laboratoire en astreinte.

Au cours de l'accident

Au moment de l'accident, le service médical doit savoir canaliser, voire apaiser le personnel toujours inquiet.

Le Laboratoire doit savoir s'organiser pour réceptionner et doser le très grand nombre d'échantillons biologiques qui lui sont transmis. Il doit disposer d'un équipe de techniciens opérationnels pour se rendre si nécessaire dans l'entreprise, afin d'y effectuer les prélèvements d'atmosphère dans les locaux de travail et éventuellement dans l'environnement (eaux, effluents divers, végétaux).

Dans l'accord formalisé il faut prévoir également les conditions de transmission des résultats du Laboratoire d'Hygiène Industrielle:

- destinataires (Médecins du Travail, Ingénieur de Sécurité, Directeur de l'entreprise, Inspection Régionale du Travail et de la Main d'Oeuvre?)
- délais, format. etc.

Après l'accident

Après l'accident, il est utile que les différentes parties intéressées (Médecins du Travail et Laboratoire d'Hygiène Industrielle notamment) tirent les conclusions du déroulement des différentes opérations afin d'améliorer si nécessaire leur collaboration pour une meilleure efficacité en vue d'un éventuel accident.

Conclusion

Notre expérience peut servir d'exemple à l'Industrie chimique où des situations accidentelles sont fréquentes.

Il nous apparait nécessaire d'attirer l'attention des autorités nationales sur l'intérêt qu'il y aurait à mettre en place des Laboratoires spécialisés en Hygiène Industrielle ayant la vocation d'intervenir dans des situations accidentelles, donc ayant reçu mission de connaître au préalable leurs conditions d'apparition.

ANALYSIS OF AN EXPLOSIVE ACCIDENT IN A VCM PLANT

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Abstract

On July 27, at 03:40 a sudden voltage drop in the IEC's power supply shut all plants at EIF-Power. Power returned after a few minutes. While restarting the VCM plant, the 500 ton refrigeration unit could not be restarted and the shift operator gave instructions to proceed with a complete EDC cracking line shut down since pressures started to rise. Inserted into the line there was a 1.5m^3 separator supposed to separate any entrained liquid EDC and to allow it to be drained. Suddenly there was a strong explosion on the ground level where this separator was installed. A considerable amount of coke, soot, EDC, HDI and VCM were ejected through the broken pipe. No fire broke out. Parts of the separator were found 100 meters away, and the major part of it landed about 15 m away reaching 15-20 m height. From the records it is certain that hot EDC gases were released at a temperature beyond their auto-ignition temperature -413°C and exploded. This gas leak may have been caused by mechanical breakage. The main drain valve of the separator was found completely detached both from the vessel and its piping, and completely plugged with fine coke dust. Unfortunately one refrigeration mechanic was a few yards away from the explosion and died 18 hours after hospitalization. Of four other VCM operators, one had to be hospitalized because of excessive gas inhalation.

Résumé

Le 27 juillet, à 3h40 une chute subite de voltage dans l'alimentation en électricité du IEC a occasionné la fermeture de toutes les usines à EIF. L'électricité est revenue après quelques minutes. Lors du redémarrage de l'usine MCV, l'unité de 500 tonnes de réfrigération n'a pu être redémarré et le préposé du quart a donné ordre de procéder à une fermeture totale de la chaîne de craquage DCE, étant donné que la pression commençait à s'élever. Il y avait un séparateur de 1.5m^3, inséré dans la chaîne, dans le but de séparer tout DCE liquide occasionné et permettre de le drainer. Soudainement, il se produisit une forte explosion au rez-de-chaussé où ce séparateur était installé. Une quantité considérable de coke, de suie, de DCE, de HCI et de MCV ont été éjectés par le tuyau brisé. Il n'y a pas eu d'incendie. On a trouvé des pièces du séparateur à

100 mètres plus loin, et la principale portion de ce dernier s'est retrouvée à 15 mètres de distance, après avoir décrit une trajectoire atteignant de 15 à 20 mètres de hauteur. D'après les dossiers, il est certain que des gaz chauds de DCE ont été relâches à des températures au-delà de leur température d'auto-inflammation de 413°C et ont explosé. Cette perte de gaz peut avoir été causée par un bris mécanique. La soupape de drainage principale du séparateur a été retrouvée complètement sectionnée, à la fois du réservoir et de sa tuyauterie, et tout à fait obstruée de fine poussière de coke. Malheureusement, un mécanicien à la réfrigération se trouvait à quelques mètres de l'explosion, et il est décédé 18 heures après son hospitalisation. Des quatres autres opérateurs de MCV, l'un d'eux a dû être hospitalisé par suite d'inhalation excessive de gaz.

A LINKED AGROMEDICAL MODEL FOR THE ASSESSMENT, INTERVENTION, AND PREVENTION OF AN OCCUPATIONAL AND RELATED PESTICIDE INJURY

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Abstract

Pesticide requirements in developing countries necessitate safe technology transfer. A linked service model has therefore been developed which integrates agrochemical and health priorities in the handling of pesticides to achieve food production needs. Introduction of this model via train-the-trainer seminar/workshops has undergone field testing in 1982 among 109 participants representing agricultural and health professionals from both the public and private sectors in Trinidad-Tobago and St. Lucia, W.I. Eighty-seven of these participants evaluated the program. Regarding program content, total scores on a scale of 0 (poor) to 3 (excellent) were as follows: Balance between theoretical and practical = 2.26; New information = 2.62; Information produced new ideas to do my work better = 2.60; Content and information was relevant to my job requirements = 2.54. Concerning training methods, scores were: Lectures = 2.38; Slides = 2.45; Question and Answer = 1.81; Pre-Post Tests = 1.59; Training Manuals = 2.69; Demonstrations = 1.49; Small workgroups = 2.30; and Case Studies = 2.30. Evaluation by the faculty stressed the need for more hands-on demonstrations, for pre- and post-seminar visits by at least one faculty member and for the use of local personnel for teaching communication skills. Changes following seminar workshops at these sites and others have included: formation of Agro-Medical Associations; provision for post-graduate education in agromedicine; improved pesticide poisoning surveillance; increased local radio and television coverage about pesticide safety; and improved pesticide disposal.

Résumé

Les besoins en pesticides dans les pays en voie de développement nécessitent un transfert de technologie de sécurité. Un modèle de services intégrés a donc été mis au point pour coordonner les priorités agro-chimiques et de santé dans la manutention de pesticides en vue de répondre aux besoins de production alimentaire. Le présentation de ce modèle à des stages d'études/ateliers visant à former des instructeurs a été mise à l'essai en milieu d'application en 1982 parmi 109 participants représentant les professionnels de l'agriculture et de la santé, issus des secteurs public et privé de Trinidad-Tobago et Sainte-Lucie, Antilles. Quatre-vingt-sept de ces participants ont évalué le programme. En ce qui concerne le contenue de programme, le pointage total sur une échelle de 0 (faible) à 3 (excellent) est le suivant: répartition entre théorie et pratique = 2.26; nouveaux renseignements = 2.62; les renseignements ont produit de nouvelles idées me permettant de mieux faire mon travail = 2.60; le contenu et les renseignements étaient pertinents aux exigences de mon travail = 2.54. Concernant les méthodes de formation, le pointage était: conférences = 2.38; diapositives = 2.45; questions et réponses = 1.81; tests avant et après = 1.59; manuels de formation = 2.69; démonstrations = 1.49; petits ateliers de travail = 2.30; études de cas = 2.30. L'évaluation par la faculté soulignait le besoin de démonstrations pratiques plus nombreuses, de visites avant et après un stage d'étude par au moins un membre de la faculté et de l'emploi du personnel local pour enseigner l'art de communiquer. Parmi les changements émanant des stages d'étude pratique à ces endroits et ailleurs, on retrouve: la présentation de nouveaux règlements, la formation de Conseils des pesticides; la formation d'associations agro-médicales; la mised sur pied de cours visant la formation en agro-médecine de diplômés universitaires; l'amélioration de la prévention contre l'empoisonnement par les pesticides; la présentation accrue par la radio et la télévision locales de sujets touchant la sécurité relative aux pesticides; ainsi qu'une meilleure élimination des pesticides.

Background

During the past decade, several problems of mutual concern to agriculture and health have surfaced in diverse areas of the world. Poor pesticide management practices, for example, have led to acute human and animal poisonings, chronic human exposure, and detrimental environmental impacts relating to pesticide persistence. Moreover, poorly integrated pesticide usage has led to premature decline in effectiveness of some pesticides; attendant increases in pest resistance have furthered the resurgence of vector-borne disease.

In the past, the University of Miami School of Medicine and the University of Oregon have responded to these problems with research, service and training activities, through their association with the Consortium for International Crop Protection (CICP). Information has been generated concerning the magnitude of the poisoning problem in Third World countries. Research on protective clothing has been conducted, and human and environmental pesticide residue determinations have been obtained. Additionally, consultations have been provided to upper and middle management pesticide professionals on an on-going basis. Chemical analyses have also been done in the area of monitoring. Finally, chemists from 56 Third World countries have participated in the University's international quality assurance program.

Training however, has been the main thrust of knowledge transfer activities. Interdisciplinary sessions, called Agromedical Workshops, have been attended by 1,634 persons from eleven countries around the world. These are shown in Table 1. Trainees have included nearly every category of agricultural and health worker, from the ministry level to hygienists and agricultural extension workers as well as personnel from the voluntary sector.

TABLE 1: Number of Participants from Third World Countries Attending Agromedical Seminar Workshops - 1972 to 1982

Country	Number of Attendees
El Salvador	78
Guatemala	175
Indonesia	205
Philippines (twice)	401
Egypt	114
Senegal	60
Colombia	300
Barbados	117
Jamaica	75
Trinidad/Tobago	77
St. Lucia	32
TOTAL	1,634

Over the past 11 years, the format of the training has been changed from a seminar/workshop to Train-the-Trainer sessions. A key to program development has been the evolution and ultimate publication of a 300 page core manual entitled An Agromedical Approach to Pesticide Management and edited by Drs. Davies, Freed and Whittemore. Over a thousand copies have been distributed to interested individuals in diverse parts of the world. Future distribution of this manual will be done by the World Bank which has also been instrumental in developing other training aids for pesticide technology transfer. A package of 500, 35-millimeter slides with an accompanying script have also been prepared and will be available for use with the core manual. First drafts of accompanying Trainee and Workshop manuals have also been designed around this book. A preliminary prototype training kit using these materials has been field tested in the Caribbean. It cannot be overemphasized that this basic core of agromedical knowledge is required for the institution of an effective program of pesticide management. Future trainers need to have a good grasp of agromedical concepts and principles and must be able to apply these to the new problems and varied conditions which they will undoutedly encounter within their respective countries.

The impact of this training has been measured both qualitatively and quantitatively. With regard to the former, numerous positive steps have taken place following the training workshops. The nature of these events has included the introduction of better pesticide safety regulations; the formation of Pesticide Boards; the formation of Agromedical Associations; the provision of post-graduate education in agromedicine; requests from physicians in many countries for specific agromedical courses; the training and appointment of the first Agromedical physician, who has since specialized and obtained a Master of Science in Public Heath degree; improved reporting of pesticide poisoning statistics; the evolution of medical seminars on the differential diagnosis of pesticide poisoning and pesticide related illnesses and institution of steps to prevent them; increased radio and TV coverage on the potential of pesticide safety in the home and field; improved pesticide disposal practices; and better communication between agriculture, health and in some cases, the chemical indsutry.

All these events have taken place and examples of each can be cited. While the current state of agromedical practice throughout the world is far from ideal, it can be stated without equivocation that a change has been effected and that an independent movement for an agromedical partnership has started.

Outcome must also be evaluated in quantitiative terms. It is only recently that attempts have been made to evaluate the training prcess more precisely. To this end, communciation experts have been introduced into the workshops. In the

Trinidad/Tobago and St. Lucia workshops, an evaluative questionnaire was prepared as well as a prototype pre-and post-test examination. Trainees evaluated the teaching program by grading their answers from zero to three. Specifically a score of three indicated complete agreement with the evaluative statement, a score of zero indicated complete disagreement and scores of one and two filled the middle ranges.

Responses from 87 of 109 participants concerning program content are shown in Table 2. The scores represent an average from attendees at seminars in Trinidad/Tobago and St. Lucia since participant response in both places was quite similar. Students felt there was a good balance between theoretical and practical information (score of 2.26), that inforamtion presented was new (score of 2.62), that the information provided both new ideas to do their own work better (score of 2.60) and to deal with pesticide problems (score of 2.68). They did not feel that the information was too general (score of 0.77) or too theoretical (score of 0.73).

TABLE 2: Participants' Evaluation of Program Content (87 of 109 Participants Responding)

Criterion	Score
There was a good balance between theoretical and practical	2.26
There was new information on the safe use and effects of pesticides	2.62
The information was too general for my purpose	0.77
The information provided me with new ideas to better do my work	2.60
The information was too theoretical	0.73
The content provided me with new information for dealing with pesticide problems	2.68

Scoring: 3 (I totally agree);
2 (I more or less agree);
1 (I more or less disagree);
0 (I totally disagree).

Responses concerning the effectiveness of training methods were also scored from zero to three, with zero representing "ineffective" and three being "extremely effective". Trainees' assessments of the various methods employed at the seminar are shown in Table 3.

TABLE 3: Participants' Evaluation of Training Methods

Method	Score
Lectures	2.38
Slides	2.45
Question and Answer Session	1.81
Pre- and Post-Tests	1.59
Training Manuals	2.69
Demonstrations	1.49
Small Workgroups	2.30
Case Studies	2.30

Scoring: 3 (Extremely effective);
2 (Very effective);
1 (Somewhat effective);
0 (Ineffective).

Lessons learned

Key principles to be followed in the future include:

1. Target audiences and training goals. Great care is needed in the selection of the target audience. Initial training should be directed at university or technical college graduate personnel since the primary goal is to establish a cadre of Third World trainers, adept at problem solving and prevention of agromedical problems, rather than simple dissemination of facts. It is particularly important to include personnel at the ministerial level. Multiple strategies for pesticide management need to be imparted.

2. Time requirements. At least two weeks of intensive training should be planned. This allows more time for demonstrations and field trips, and will enhance program capacity for successful technology transfer.

3. Post seminar follow-up. Lack of follow-up is a serious weakness. It is important to work with newly educated trainers as they attempt to organize teaching programs. Furthermore, continuous contact should be made with the trainers to keep them appraised of new developments in the field of pesticide safety.

4. Communication skills. Training must strive not only to communicate technical information and approaches to problem solving and prevention, but also should also impart the skills of communication which are so necessary to technology transfer. The faculty is strengthened by the addition of a communications expert. Moreover, in order to recognize cross-cultural differences, the services of an in-country communications expert should be available when the new trainers establish workshops in their own countries.

5. Evaluation. Evaluation of the program is clearly important. Immediate impacts (learning knowledge gains) and longer term effects such as use of the teaching materials, new legislative and monitoring activities, presence and/or growth of the agromedical network, the future potential of agromedical associations, need to be monitored. Further, the committment of the Third World nation itself needs to be accounted for in the evaluative effort.

Guiding principles

Assumptions underlying what will be taught include:

1. Pesticides will continue to be used for agricultural purposes, probably on an increasing scale in developing countries where population increases are outstripping food production. Hence we cannot and should not look forward to the abolition of pesticides in the foreseeable future.

2. A realistic balance must be struck in the curriculum between the agro-imperative needs of pesticides, and the threats to personal and public health. The students must see pesticides in the wider scheme of things, that is, an increasingly pervasive and persistent attempt to control agro-pests which is needful in the mid-term until other supplementary control measures appear.

3. A broader public interest must be recognized in the use of pesticides, namely, that personal, community, and public health risks are real and present dangers, and that non-target organisms can be unintended victims.

4. A phenomenon exists by which the use of pesticides contributes to the vectors of human disease (and domestic animals) becoming resistant to those self-same pesticides and making control of these diseases exceedingly difficult, eg. malaria, dengue fever and yellow fever. Promiscuous use of these chemicals is not in the interest of either agriculture or human health.

5. Empathy for both sides, agro and health, must be engendered. There are no good or bad guys -- both need to recognize the imposed needs and requirements of the other. We and they become "us" -- working together to feed humanity and keep it healthy.

This teaching program then, should be done in the context of the need for improving pest management and safe, effective use of pesticides.

THE POSSIBILITIES OF ACCIDENTS WITH CHEMICAL SUBSTANCES - THEIR EFFECTS ON HUMAN BEINGS AND THE NECESSARY EMERGENCY MEASURES

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Abstract

The tragic consequences of major catastrophes arouse attention and attract sympathy in all quarters. The question of blame does not arise if a natural catastrophe is concerned but is immediately raised and vehemently discussed if chemical substances cause injury within and without chemical production sites. It cannot be denied that the chemical industry processes enormous amounts of potentially hazardous substances, which may be toxic, combustible, explosive or simply cause injury to the skin. As a result of the highly developed safety engineering techniques and intensive monitoring, grave accidents have become extremely seldom. Nevertheless, we must always reckon with the possibility of a catastrophe occurring when unfavourable conditions coincide, including in particular the human element. The most important substances that are liable to cause serious accidents as a result of their physicochemical properties must be known to the plant physician, and are therefore explained in detail. Fires and explosions often cause a chain of grave reactions in chemical production plants which add up to a catastrophe. Human beings involved in such accidents are usually in a state of polytrauma; in other words, they suffer from: fractures, contusions, compressions, bruises with symptoms of shock, damage caused by explosion to the lungs and the intestines, in particular the colon, burns of varying degrees, and grave complications of the lung in the case of gas eruptions, alone or together with exposure to hot air and steam. The most efficient first aid measures, and the optimum organization of emergency stations, etc., are factors of decisive importance for the fate of the victims of all such accidents. These are discussed in detail.

Résumé

Les conséquences tragiques des catastrophes majeures attirent l'attention et la sympathie dans tous les milieux. Il n'est pas question d'attribuer un blâme s'il s'agit d'une catastrophe naturelle mais si des substances chimiques

occasionnent des accidents ou blessures à l'intérieur ou l'extérieur des secteurs de production chimique, la question est immédiatement soulevée et fortement débattue. On ne peut nier que l'industrie chimique transforme d'énormes quantités de substances potentiellement dangereuses, qui peuvent être toxiques, combustible, explosives ou simplement causer des blessures à peau. Grâce aux techniques très avancées d'ingénierie de la sécurité et à un contrôle intensif, les accidents graves sont devenus extrêmement rares. Néanmoins, nous devons toujours reconnaître la possibilité qu'une catastrophe se produise lorsque des conditions défavorables sont réunies, y compris, en particulier, l'élément humain. Les substances les plus importantes qui sont susceptibles de causer de graves accidents, étant donnée leurs propriétés physico-chimiques, doivent être connues du médecin de l'usine, et sont donc expliquées en détail. Les incendies et les explosions causent souvent une chaînek de réactions graves dans d'autres usines de production chimique ou réservoirs d'emmagasinage, qui finit par produire la catastrophe.

Les humains qui se trouvent pris dans de tels accidents sont habituellement dans un état de traumatisme; en d'autres mots, ils souffrent de fractures, contusions, compressions, ecchymoses avec symptômes de choc, dommages aux poumons et aux intestins, en particulier au colon, causés par l'explosion, brûlures à divers degrés, graves complications pulmonaires dans le cas d'éruption de gaz, seul ou associé à l'exposition à l'air chaud et à la vapeur. Les mesures les plus efficaces de premiers soins, et l'organisation optimale de stations d'urgences, etc., sont un facteur d'importance décisive pour le sort des victimes de tels accidents. Ces mesures sont traités en détail.

Introduction

When a major accident occurs in civilian life, we usually call it a catastrophe. These accidents occur unexpectedly, cause brutal damage and destruction to human beings and material, and leave everybody with a feeling of shock. The press reports all details of the catastrophe and illustrates these reports with gruesome photographs. The propane gas explosion on January 4th, 1966 in Feyzin, France, which killed 12 people, shocked the whole world and even worse were the chain explosions with their terrible consequences in the holiday camp of Los Alfaques south of Tarragona on July 11th, 1978. The catastrophe began with the explosion of a road tanker loaded with propylene near the holiday camp; this ignited the butane gas flasks and the parked cars in the camp. A wave of fire engulfed an area approximately 150 m long and 40 to 50 m wide, destroying everything in its path. Another terrible accident was the explosion of fuel tanks in the Venezuelan power plant Tacoa near Caracas, which killed over 153 people.

The analysis of these accidents put the blame on technical and human failure. Despite constantly improved safety precautions and intensive training of the personnel to promote safety consciousness, catastrophes are always liable to occur. For the industrial physician, this means that he must devote himself to intensive study of the causes and effects of such catastrophes and the most effective form of therapy.

In order to understand the process of large-scale accidents caused by chemicals, the industrial physician must have a sound knowledge of the physicochemical properties of the potential substances.

In principle, every substance can occur in three physical states: solid, liquid, and gaseous. It is characteristic for the liquid-vapour transition field that there is always a definite pressure, which we call the vapour pressure, over the liquid as long as the temperature remains constant; the degree of this pressure is, therefore, independent of the ratio between the two phases. This vapour pressure increases markedly with rising temperature. This physical fact must be taken into consideration in estimating the risks involved by flammable and biologically active liquids.

Fire and explosion hazards

A fire can always break out when fuel, atmospheric oxygen, and a minimum temperature are present at the same time and at one spot.

If one of these conditions are not fulfilled, no accident can occur. It is obvious that any precautions for fire prevention must be aimed mainly at controlling the components fuel and elevated temperature, because the exclusion of air is a far more difficult undertaking.

When the fuel is present in a very fine state of dispersion in the air, as is always the case when flammable dusts (e.g. flour, sugar, or wood dust), or flammable gases (methane), or the vapours of flammable liquids are mixed with air within certain limits, the reaction with atmospheric oxygen initiated by the elevated temperature takes place within a fraction of a second; in other words, an explosion occurs. Chemically, fires and explosions are oxidation processes, whose duration depends on the degree of dispersion of the fuel in the air. (Explosives and fuels which contain in their molecules the oxygen necessary for reaction will not be included in this discussion.)

The vapour pressure of a liquid is the cause of the formation of a steam-air mixture above the level of the liquid and in accordance with the temperature; this vapour-steam mixture is ignitable under certain conditions. For flammable liquids, these conditions are defined by the lower and upper explosion points. These two points are the temperatures of a flammable liquid at which the concentration of the saturated vapour-air mixture, at a total pressure of 1013 mbar, reaches the lower or the upper explosion limit. The lower explosion point, which is practically the same as the flash point, is determined by the standardized Abel-Pensky and Pensky-Martens methods of determining the flash point. Flash points below 65°C are measured by the Abel-Pensky method in instruments with closed crucibles, while flash points above 65°C are measured by the Pensky-Martens method in instruments with open crucibles.

Below the flash point, the concentration of vapour in the vapour-air mixture is too low, and above the upper explosion point, this concentration is too high, so that ignition is not followed by progressive combustion. For flammable gases, the analogue to the lower and upper explosion limits is the ignition range.

In our motorized age, all of us have to do with carburetor fuels almost daily, and we should therefore know that the flash point of these fuels is around -20°C. This means that it is only in extremely cold weather that a dangerous explosive atmosphere may be present in the fuel tank of a private car. In all other seasons of the year, the concentration of vapour in the vapour-air mixture is too high, or in other words, above the upper explosion limit of 7% by volume of vapour in the air.

Diesel fuel and Fuel Oil No. 2 or Class D Fuel Oil, which are also things that many of us have to deal with every day, have a flash point of +55°C. This means that, in our temperate zone, there can never be a dangerous explosive atmosphere in these fuel tanks. It is impossible to set Fuel Oil No. 2 or Class D Fuel Oil on fire without heating it first with a cigarette lighter. However, if we atomize the Fuel Oil No. 2 or Class D. Fuel Oil or the Diesel fuel, it can ignite at any time without preheating, because the fuel is now present in a finely dispersed form in the air.

The degree of danger involved by flammable liquids is characterized by the flash point. It is not surprising, therefore, that in the industrial countries, more or less restrictive regulations depending on certain limiting temperatures have been established for handling flammable liquids. In West Germany, these liquids have been classified for the last 80 years in classes with flash points below 21°C, from 21°C to 55°C, and from 55°C to 100°C. In the U.S.A, which is so huge that subtropical environmental temperatures also have to be taken into consideration, they differentiate between classes with flash points below 0°C, from 0°C to 21°C, from 21°C too 35°C, from 35°C to 53°C, and over 53°C.

The flammability is, however, not the only property of these liquids that involves a hazard for human beings. The vapours may also be toxic, benumbing, or caustic. Under all conditions, therefore, inhalation of the vapours and, in general, any contact with these liquids must be avoided. In order to ensure this, the packaging used to transport and store these liquids must fulfill certain specifications.

The dangerous inorganic and organic substances are listed in the following tables (Tables 1-5). The gaseous substances are specially marked.

TABLE 1: Explosion Limits and Flash Points of Inorganic and Organic Substances

Substance	Explosion limits % in mixture with air		Flash point in °C		Spontaneous combustion temperature in °C
	Lower	Upper	Closed crucible	Open crucible	
*H_2	4.1	74.2	–	–	580
*H_2S	4.3	45.5	–	–	–
*NH_3	16	27.0	–	–	780
*CO	12.5	74.2	–	–	651
CS_2	1.0	60.0	–30	–	102
*COS	11.9	28.5	–	–	–
HCN	5.6	40	–	–	538

* Gaseous substances

Hommel, "Handbuch gefährlicher Güter" and Industr. Enging. Chem. 22, 881

TABLE 2

Substance	Explosion limits % in mixture with air		Flash point in °C		Spontaneous combustion temperature in °C
	Lower	Upper	Closed crucible	Open crucible	
*Methane	5.0	15.0	–	–	537
*Ethane	3.0	12.5	–	–	510
*Acetylene	2.5	80	–	–	335
*Propane	2.12	9.35	–	–	466
*Propylene	2.0	11.7	–	–	455
*Butane	1.86	8.41	−60	–	430
Pentane	1.4	7.80	< −40	–	309
n–Hexane	1.18	7.40	−22	–	247

* Gaseous substances

TABLE 3

Substance	Explosion limits % in mixture with air		Flash point in °C		Spontaneous combustion temperature in °C
	Lower	Upper	Closed crucible	Open crucible	
Cyclohexanone	1.26	7.75	−18	–	269
Benzene	1.4	7.10	−11	–	580
Heptane	1.1	6.70	4	–	233
Toluene	1.27	6.75	4	7	549
Xylene	1.0	6.0	17	24	469
n–Dekane	0.77	5.35	46	–	260
*Natural gas	4.8	13.5	–	–	–

TABLE 4

Substance	Explosion limits % in mixture with air		Flash point in °C		Spontaneous combustion temperature in °C
	Lower	Upper	Closed crucible	Open crucible	
Methyl chloride	8.2	19.4	–	–	625
Ethyl chloride	3.6	14.8	-50	-43	538
Ethyl bromide	6.75	11.25	–	–	511
1.2-Dichloroethene	6.2	15.9	13	18	413
1.2-Dichloroethylene	9.7	12.8	6	–	460
1.1-Dichloroethylene	5.6	13	14	–	458
1.2-Dichloropropane	3.4	14.5	15	18	558
Methanol	6.0	35.5	12	16	400
Ethanol	3.28	19	11	–	426
Acetaldehyde	4.0	57.0	-27	–	156
Acetic Acid	4.0	–	40	43	568
Methyl formate	5.0	22.7	-19	–	449
n-Propanol	2.5	–	15	29	433
i-Propanol	2.5	–	12	16	455
Acetone	2.15	13.0	-18	9	604
Methylethyl ether	2.0	10.1	-37	–	190

TABLE 5

Substance	Explosion limits % in mixture with air		Flash point in °C		Spontaneous combustion temperature in °C
	Lower	Upper	Closed crucible	Open crucible	
Ethyl formate	3.5	16.5	-20	-12	440
Diethyl ether	1.7	48	-40	–	186
Methylethyl ketone	1.81	11.55	- 1	–	505
Divinyl ether	1.7	27.0	-30	–	360
1,4-Dioxane	1.97	22	18	–	375
Butanol	1.68	–	28	–	441
Pyridine	1.8	12.4	20	–	573
*Ethylene oxide	2.60	100.6	-18	–	440
Propylene oxide	2.6	22	<-44	–	430
Otto fuel	0.6	8	-20	–	220
*Vinyl chloride	3.8	22	–	–	472

In mass accidents caused by chemical substances, it can be assumed that most of the victims are polytraumatized. Polytrauma is a simultaneous multiple injury of a single or several organ systems and/or different parts of the body. An acute vital hazard may be the consequence of one injury alone, or the combination of several injuries. Generally speaking, polytraumatized victims are in a hypovolaemic state of shock, the intensity of which varies. The polytrauma severity degrees according to Schweiberer (4) are useful in estimating the danger in which these patients are (Table 6).

Severity degree I is defined by light injuries, contusions, and uncomplicated fractures, and by an absence of a state of shock.

Severity degree II covers severe injuries, comminuted fractures, soft-tissue injuries, and a light state of shock, but no acute vital hazard.

TABLE 6: Polytrauma Severity Degrees (Schweiberer, 1978)

Severity degree I

Light injuries, contusions, uncomplicated fractures, no state of shock

Severity degree II

Severe injuries, comminuted fractures, soft-tissue injuries, light state of shock, no acute vital hazard

Severity degree III

Massive haemorrhagic shock, severe thorax and abdominal cavity injuries, severe craniocerebral trauma, multiple fractures

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Severity degree III applies to massive haemorrhagic shock, severe thorax and abdominal cavity injuries, severe craniocerebral trauma, and multiple fractures.

Besides the severity degree, the loss of blood is a very significant factor in making a prognosis. The loss of blood initiates the state of shock with centralization of the circulation, which in its protracted course leads to tissue hypoxia and acidosis, increased capillary permeability, stasis and interstitial edema, and finally through vasodilation to decentralization and irreversibility of the state of shock. It is difficult to estimate the loss of blood, because it may vary widely in the individual parts of the body (Figure 1). The best method is to use Allgöwer's "shock index", according to which the loss in volume can be calculated by the formula:

$$\frac{\text{Pulse rate (beats per minute)}}{\text{systolic blood pressure mm/Hg}}$$

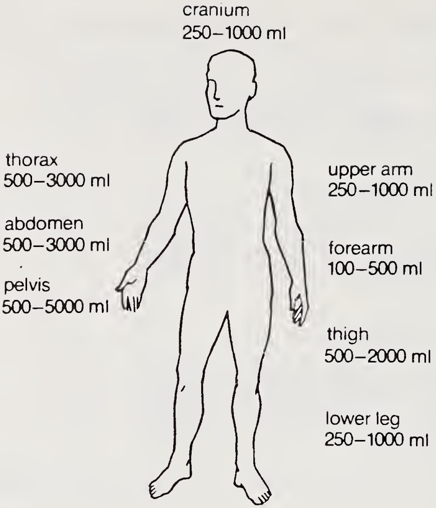

Figure 1: Possible Losses of Blood Due to Injuries to the Body Cavities and Fractures

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Shock index

A shock index of 1.5 indicates an average loss of blood of 30–35%; an index of 2 indicates a loss of 40–45%, and an index higher than 2 indicates a volume loss of more than 50%, i.e. more than 3 litres of blood, which in an acute state of shock leads within a few minutes to ventricular fibrillation, followed by asystole and finally exitus lethalis.

All experience to date indicates that the prognosis of the polytraumatized patient depends not only on the severity degree of the injury and the injury combination, but also on the shock index and the duration of shock. The sooner a patient undergoes first aid treatment, the greater are his chances of survival. According to a statistical investigation (1), none of the patients who had been treated within 15 minutes died. After 30 minutes of waiting time until the victim was given medical care, the mortality rose to 16.7% after 45 minutes, it increased to 33.3%, and after 60 minutes, it rose to 50%.

This means that the polytraumatized patients in a state of shock must be given an infusion immediately and undergo surgical treatment as soon as possible.

Blast injuries

When explosions occur, injuries caused by the blast (5) are to be expected. The higher the rate at which the blast strikes the victim, the greater the injury. The blast waves cause a destruction of the interior structures in the organism, and particularly in the lungs and other air-filled organs, including primarily the large intestine, as a result of the implosion effect. This has effects on the lung parenchyma, which corresponds physically to a liquid, and on the air in the alveoli. Similar physical conditions and reactions occur in the intestines, but to a lesser extent in the other organs. A severe blast injury results in a lung contusion with haemorrhagic alveolar and interstitial edema, microatelectases with increase of the intrapulmonary dextrosinistral shunt, and a corresponding arterial hypoxia. This complex finally results in a progressive ventilatory insufficiency.

Injuries of the lungs caused by an explosion show anatomic-pathological destruction through rupture of tissue and angiorrhexis and dilation of the right heart. Arterial air embolism can also be detected in the cerebral and coronary vessels. Rupture of the pulmonary vessels with haemorrhage and haemoptysis, air embolism and ventilatory insufficiency are the reasons for the rapid death. Rupture of the intestines, and particularly of the large intestine, may also play a role.

The victims usually complain of a sudden pain in the chest, acute abdominal and testicular pain, nausea, retching, earache, impaired hearing, and weakness in the extremities. Clinically outstanding symptoms are shortness of breath, haemoptysis, chest pain, cyanosis, bronchitic sounds, signs of haemothorax and pneumothorax, with or without emphysema of the skin.

The most severe injuries caused by blast show a progressive ventilatory and cardiac insufficiency with tachycardia and decreased blood pressure accompanied by a state of shock.

The symptoms of an acute abdominal injury may show, in addition, destruction in the abdominal cavity with rupture of the intestine. In this case, as mentioned above, it is the large intestine that is most often injured because of its air content. Injury of the small intestine and the parenchymal intra-abdominal organs are less frequent.

Apart from the primary clinical diagnosis, the radiological examination of the chest provides a conclusive diagnosis. In this connection, it must not be forgotten that changes of the lungs, analogous to the other lung contusions, can sometimes only be identified after one to four weeks, although they can usually be diagnosed within 24 to 48 hours. Pulmonary infiltrates, pulmonary edema, pneumothorax and haemothorax, mediastinal and pulmonary emphysema, and cardiac dilation are to be expected. Further symptoms that must be examined clinically are arterial air embolism and extrathoracic injuries. ECG, blood gas analysis, haemoglobin estimation and haematocrit readings are necessary diagnostic aids.

The therapy is oriented to the clinical symptoms. If these symptoms indicate a danger to life, the therapeutic measures commonly adopted are shock therapy to remove the hypovolaemia, endotracheal intubation to keep the respiratory passage open, supportive treatment of the heart, and in some cases the head down position (Trendelenburg's position) to prevent cerebral air embolism. Haemothorax and pneumothorax require thorax drainage to offset the intrathoracic pressure, and thus to staunch the bleeding. As an intial treatment, it is advisable to use the Tiegel tube with valve. In cases of abdominal injuries, a stomach tube must be applied and if necessary the surgical prognosis must be made, as soon as possible.

In the case of lung contusions without respiratory insufficiency, early artificial respiration is indicated. In severe cases with respiratory failure, it is advisable to administer early mechanical respiration with positive end-expiratory pressure (PEEP) and shock therapy, to maintain the oncotic pressure in the intravascular space, with a 20% solution of human albumin; this should be accompanied by an immediate large-dose administration of an adrenocortical steroid, e.g. 1 g of methylprednisolone, and a salidiuretic medication to prevent a transfusion lung. If there is any danger of a pneumothorax, thorax drainage should be applied a priori. Another danger involved in positive pressure respiration is the possibility of air embolism. For this reason, the positive end-expiratory pressure must be constantly controlled and it must be kept as low as possible.

In a catastrophe, no differentiated form of therapy is possible. Emergency therapy consists of the shock treatment of victims with lung injuries, the alleviation of pain, positioning or bedding of the victims, oxygenation, and thorax drainage for intrathoracic pressure compensation.

Emergency treatment
of explosion injuries

1. Shock treatment
2. Pain relief
3. Oxygen supply
4. Storage
5. Thorax drainage
6. Introduction of stomach tube
   and if necessary laparotomy

Thermic and thermochemical injuries

Thermic and thermochemical injuries (7,8,9,10) are also normal consequences of mass accidents. For the prognosis and the therapy, the degree and the area of the burn are of decisive importance. The depth effect in the tissue depends on the temperature and the exposure time. A short-term exposure to high temperature, as occurs in an explosion, usually has a lower depth effect than a longer exposure to a lower temperature. Exposure to temperatures of 50 - 60°C can cause a second-degree histological lesion, and higher temperatures may cause third-degree histolysis. A short-term exposure to hot liquids causes second-degree injuries, while short-term exposure to flames or liquid metals causes third-degree burns.

An exact determination of the histological lesion at the place of the accident is often difficult owing to contamination of the wound, and should therefore be done in the hospital. The area of the burn is, however, visible at a glance, and it can be determined by Wallace's method (Figure 2). If the victim is a child, the relation between the head and the body according to his or her age must be taken into consideration (Table 7).

Besides the thermic injuries, the possible absorption of toxic substances and further sequelae of the accident must be taken into consideration in administering first aid. If the victim has suffered face injuries, inspection of the nasopharynx and the respiratory tract is absolutely necessary. The upper respiratory tract, in particular, is very often involved.

Complications of this kind must always be expected if the burn has been caused by superheated steam or by an accident in an enclosed room. Inhalation of hot air causes damage to the tracheal mucous membrane extending even to the bifurcation, while superheated steam and smoke particles damage the lungs. In all such cases, therefore, endonasal intubation should be carried out immediately, because edema is otherwise liable to occur within a short time. The intubation must last for at least 48 hours.

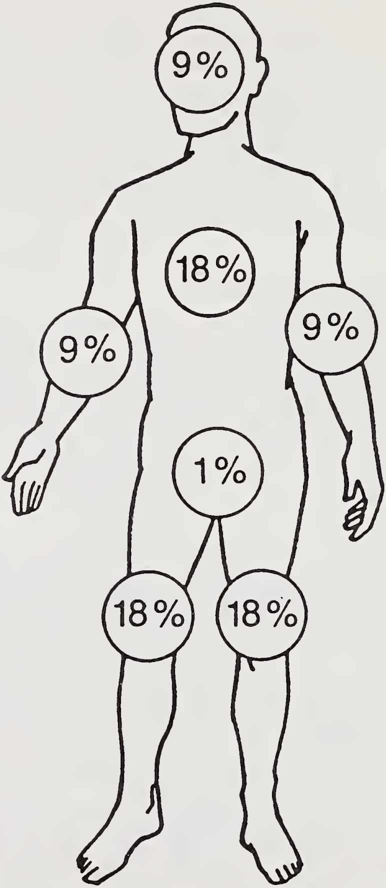

Figure 2: Nine-Percent-Rule (Wallace) for Adults

TABLE 7: Nine-Percent-Rule as to Parts of the Body and Age

Adults		Children				
	burn (2°/3°)	1 year	1-4	5-9	10-14	15
7	head	19	17	13	11	9
2	neck	2	2	2	2	2
13	trunk (front)	13	13	13	13	13
13	trunk (back)	13	13	13	13	13
2.5	r. gluteal region	2.5	2.5	2.5	2.5	2.5
2.5	l. gluteal region	2.5	2.5	2.5	2.5	2.5
1	genitalia	1	1	1	1	1
4	r. upper arm	4	4	4	4	4
4	l. upper arm	4	4	4	4	4
3	r. forearm	3	3	3	3	3
3	l. forearm	3	3	3	3	3
2.5	r. hand	2.5	2.5	2.5	2.5	2.5
2.5	l. hand	2.5	2.5	2.5	2.5	2.5
9.5	r. thigh	5.5	6.5	8	8.5	9
9.5	l. thigh	5.5	6.5	8	8.5	9
7	r. lower leg	5	5	5.5	6	6.5
7	l. lower leg	5	5	5.5	6	6.5
3.5	r. foot	3.5	3.5	3.5	3.5	3.5
3.5	r. foot	3.5	3.5	3.5	3.5	3.5
	sum					
	total burn					

A severe complication of the burn is the state of shock, which cannot be distinguished from that of the polytraumatized patient. It is caused mainly by volume loss. Whether a burn toxin is also involved is a question that has been discussed, but there is no clinical proof for its presence or absence. Both hypvolaemic haemorrhagic shock and burn shock are replaceable, but the difference between the two is that burn shock cannot be influenced therapeutically because of its intravascular volume loss into the interstices and/or at the body surface, which may last for several days. An immediate, forced infusion to treat the protracted burn shock with its serious volume deficiency is an essential first aid measure, because if it is not done immediately, it cannot be corrected hours later. Anatomic-pathological investigations indicate that many delayed fatalities occurring 10 - 14 days after the accident were due not to an infection or the effect of a toxin, but solely to the irreversible state of shock initiated by the inadequate initial treatment. Suitable infusion solutions are plasma-protein solutions, or if these are not available, plasma-expanders in combination with electrolyte solutions. After alleviation of the pain and application of the infusion, the patient should be transported immediately on a foamed rubber or plastic bedding or an ambulance sheet without any wound dressing to the hospital. Any chemical solutions must be rinsed off before the patient is transported.

Coloured bactericidal solutions for wound disinfection are contra-indicated, because they make it difficult for the physician in the hospital to estimate and treat the wound.

Chemical accidents

Chemical accidents usually involve chemically irritative or toxic gases, vapours, or smokes (6). The extent of the inhalation reaction with the irritative substances depends on their concentration and water-solubility. In low and medium concentrations, lung irritants that dissolve readily in water, e.g. ammonia and hydrogen chloride, react very rapidly with the mucous membranes of the upper respiratory tracts. In contrast, those with medium water-solubility are liable even in the same concentration to damage the respiratory tract through the bronchial system. Massive doses of these water-soluble substances are also able to penetrate into the alveolar space and cause an additional lung edema. The toxic lung edema is, however, typical for the effect of substances with low water-solubility and high lipoid-solubility, e.g. phosgene and nitrous gases. The irritation of the mucous membranes of the upper and middle respiratory tract is insignificant or slight, depending on the concentration of these substances. The decisive factor is the lesion of the alveolar-capillary limiting membranes with consequent lung edema, which only occurs after an interval of several hours.

The clinical picture corresponds to the pathogenetic mechanism of the water-soluble and lipoid-soluble lung irritants. The water-soluble substances cause a visible and stethoscopically detectable irritation of the respiratory tract, and require symptomatic therapy with cough-relieving medication. The clinical signs of the effect of lipoid-soluble irritants are very slight in the initial phase, and in most cases, consist only of slight irritation of the mucous membranes. After some hours, however, toxic lung edema may develop, according to the concentration, as mentioned above; the early diagnosis of this edema is best carried out radiologically.

On exposure to massive doses of these substances, pulmonary changes can be detected after 2 - 6 hours, and after exposure to small doses, after 8 - 12 hours. The treatment must take the latent phase into consideration, and this means supervision of the patient for 24 - 48 hours. Complete bodily relaxation, tranquillization with benzodiazepine derivatives, cough relief, and prevention of the edema with an adrenocortical steroid are necessary during this period. If lung edema is to be expected in view of the exposure, or if it can be detected radiologically in its early stage, adrenocortical steroids in relatively large doses corresponding to 100 - 250 mg of prednisolone up to a total dose of 1 g should without hesitation, be injected by the intravenous route, in order to counteract the hyperpermeability. The additional inhalation of oxygen in a dose of 2 - 4 litres per minute is beneficial in improving the oxygenization and decompression of the pulmonary circulation. Diuretics are contra-indicated, as in the treatment of burns, because they would actually increase the present haemoconcentration. The cardiac supportive treatment with digoxin derivatives may be necessary in prolonged clinical treatment to support the dextrocardia which has been stressed by the intrapulmonary pressure increase; it may also be necessary as prophylaxis for older patients. When these first aid measures have been carried out, and a report on the accident with indication of the causal agent has been made, the patient can be transferred to the hospital.

In order to be fully prepared for mass accidents or catastrophes, precise and comprehensive planning, organization, and repeated training of the emergency personnel and all emergency organizations are essential (2,3). This organizational basis cannot, however, develop optimum efficiency unless clinically experienced physicians with sound technical and scientific knowledge are available. One of these physicians, namely the one with the most experience, must act as the medical head of the emergency squad and be responsible for selection of the victims. With good teamwork and well trained personnel, it should then be possible to keep all damage done down to a minimum.

Summary

No matter what safety measures are adopted, unexpected catastrophes will always occur. The industrial physician must, therefore, know the potential causes and the effects of a mass accident with chemical substances, and the emergency treatment for the types of injuries to be expected. Information is therefore offered on:

1. Dangerous substances with their physicochemical properties.
2. The polytrauma to be expected in emergency cases.
3. The effects of explosions on the air-filled organs, lungs and intestines, and their therapy.
4. The thermal and thermochemical injuries and the clinical problems involved.
5. The special problems involved by the action of lung irritants.

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WHY A DISCUSSION ABOUT "INTOXICATIONS THROUGH NITROGLYCOL" AGAIN?

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Abstract

I observed three deaths through chronic inhalation of nitroglycol by explosives workers. My publications on this matter thirty years ago were confirmed, especially from abroad. One result of my investigation was that these deaths were recognized as occupationally caused with regard to insurance law. Experiments showed that the way nitroglycol affects animals differs from the way it affects humans. The biological processes of nitroglycol inhalation will be briefly dealt with. The total elimination of the inhalation possibility is crucial for occupational hygiene surveillance. This was carried out under my observation in a factory in which the inhalation of nitroglycol no longer occurred. Since then the chronic headaches of the explosives workers and the fatal incidents have ceased. But according to reports concerning this topic at the 1982 Medichem conference in Paris, the explosives workers are obviously still exposed to the harmful inhalation of nitroglycol in many countries.

Not the doctor but the technician of industrial safety has the say with regard to preventive measures. The doctor has to "pass the buck" to the technician. His measures are responsible for the well-being of the explosives workers. This is a development which is gaining importance in many areas of industry. But especially here it is crucial.

Résumé

J'ai observé trois décès causés par l'inhalation chronique de nitroglycol chez des travailleurs du secteur des explosifs. Mes publications sur le sujet, il y a trente ans, ont été confirmées, particulièrement à l'étranger. Un résultat de ma recherche a été que, du point de vue de la loi sur les assurances, le milieu de travail a été reconnu comme ayant contribué à ces décès. Les expériences ont montré que les effets du nitroglycol ne sont pas semblables chez les animaux et chez l'homme. Le processus biologique de l'inhalation de nitroglycol sera traité brièvement. L'élimination totale de la possibilité d'inhalation est cruciale pour le contrôle en hygiène professionnelle. Cette tentative a été réalisé avec ma collaboration dans une usine où l'inhalation de nitroglycol ne se produit plus. Depuis ce contrôle, les maux de tête des

travailleurs du domaine des explosifs et les incidents fatals ont cessé. Mais d'après certains rapports relatifs à ce sujet, présentés à la conférence Medichem 1982 de Paris, les travailleurs du domaine des explosifs sont, de toute évidence, toujours exposés à l'inhalation nocive du nitroglycol dans plusieurs pays.

C'est le technicien à la sécurité industrielle et non le médecin qui doit appliquer les mesures de prévention. Le médecin doit lui inculquer les principes. Ses mesures sont responsables du bien-être des travailleurs du domaine des explosifs. C'est une orientation qui gagne en importance dans plusieurs domaines de l'industrie. Mais elle est particulièrement cruciale dans le secteur à l'étude.

Background

Three reports about nitroglycol were given at the last Medichem conference in Paris in 1982. They showed that the nitroglycol problem in dynamite factories has apparently not been solved yet. After the war a number of deaths occurred in the explosives factory in the state of Saarland. I investigated these sudden deaths of the dynamite workers. It turned out that the workers were excessively exposed to the fumes of nitroglycol. Nitroglycol is an excellent waterproof explosive with particularly excellent, technical qualities. However, all of the workers exposed to it suffered from incessant, acute headaches. Also a kind of bradycardia and hypotension were noticeable. The deaths only occurred after one or two days off work before entering the production rooms once again ("Monday illness").

There was great discussion, unrest, and scientific debate. I reported these events in publications. All three cases were recognized in Germany as work-caused deaths for insurance purposes. I was then afterwards informed that the same observations were made in the United States, Canada, and South Africa. My reported events were confirmed in writing, however, it was often mentioned that no publications were made until then in order to avoid social-political unrest among the workers (information from Eddy, South Africa; Haslam, Canada; and authors from Italy and Scandinavia).

One tried to explain the sudden deaths of the dynamite workers outside of the nitroglycol atmosphere as "withdrawal symptoms" or as vasomotoric results from an accumulation of nitroglycol in the circulation. The animal experiments of my assistant Stein showed that the different species like the cat as a flesh-eating animal and the rabbit as a plant-eating animal react and become ill differently than the human.

In humans no hemoglobin and no intraerythrocytic Heinz bodies are formed. The pathologic-functional events were not scientifically explained by the animal experiments, even though it was clinically conducted in the exact same causal manner.

Last year in September 1982 three new reports about the effects of nitroglycol were given at the Medichem conference in Paris, to be more precise, from French investigations in Roun, Marseille, and Lille, as well as from a Spanish investigation by Carlos de Torregrosa in Navarro in southwestern Spain. Uniformly, but independently of one another, these investigations verified the clinical events that I published and demanded that such occupational deaths receive recognition for medical insurance, which is not the case in France. They believe they have electrocardiographically shown the explanation of the events to be a "withdrawal syndrome". Repolarization abnormalities in the electrocardiogram were verified during the "withdrawal phase". They diminish during the first hour of the new exposure, as in test results. These investigations suggest a pathological "withdrawal syndrome" in the dynamite workers.

Conclusions

What conclusions did we draw from these observations at that time?

The technical and hygienic situation of the work in this trade changed radically. The inhalation of nitroglycol fumes were completely eliminated after this time. As a result of our observations the dangerous fumes were completely removed. The so-called Drais-mixing process was conducted with a ring-edge fume exhaust. Earlier, (when entering the workroom) there had been an intensive smell of nitroglycol. After alterations, there was no noticeable smell of nitroglycol fumes. The mixing process as well as the cartridging were carried out automatically so that no worker needed to enter the room. That is to say, all of the processes which were earlier carried out by hand were completely eliminated. The nitroglycol had also affected the workers through skin absorption. They seldom wore the gloves they were provided with. Thanks to automation this also was completely eliminated.

Since this time the workers have no longer complained about headaches. Fatal incidents have not occurred since 1950. In closing, everyone must strive for better cooperation between medicine and technical safety. The doctor must "pass the buck" to those responsible for technical safety and have them participate to a greater degree in the area of prevention. There are so many practical examples of this. The nitroglycol problem has been solved for this work situation. Wherever the effects of nitroglycol turn up, the doctors have to reject all personal blame as unjustified. The technicians now have the say.

THEME III

APPLICATIONS OF COMPUTER TECHNOLOGY IN OCCUPATIONAL HEALTH

APPLICATIONS DE LA TECHNOLOGIE INFORMATIQUE A LA SANTE PROFESSIONELLE

COMPUTERS IN OCCUPATIONAL HEALTH: PRESENT AND FUTURE APPLICATIONS AND CONCERNS FOR INFORMATION AND ADVICE

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Introduction

Like society as a whole, the occupational health community is confronted by issues concerning the current and future development of computer and related microelectronic technologies.

We must ask some obvious yet important questions, and try to provide at least tentative answers. Is this development needed in occupational health, or is it a technological boondoggle? Are we getting a new tool promising solutions to many of the existing problems in occupational health, or are we simply creating a new set of problems for ourselves? In attempting answers to these questions, we should begin by identifying the essential function of computers, the essential function of occupational health, compare these, and then identify the concerns which have already surfaced or which might do so in the future. This is the approach adopted in this paper, with the exception that occupational health sometimes provides too broad a canvas, so that we have in places limited the analysis to occupational health services. In that these are part of occupational health, the analysis does have relevance to the broader field.

Because computers are spreading so rapidly, there is a need to evaluate existing experience, and that of the Canadian Centre for Occupational Health and Safety (CCOHS) is relevant. We see the computer as a development which can help to solve many problems in occupational health but not without creating some new ones; whence, the concerns. The purpose of our paper is to identify the concerns not to allay them, though we do suggest things which we should like to see done.

Essential functions of computers relevant to occupational health

At present, computers have at least six functions relevant to occupational health:

1. compilations of words and numbers, such as medical records;
2. record linkage among the compilations; computations of the records for epidemiological and other purposes;

3. instrument and other data processing;

4. information/data retrieval from on line indexes or from compilations of data and other knowledge;

5. communication by electronic means; and

6. education.

The first three correspond to the uses of computers in occupational health to be addressed elsewhere in these proceedings by Dr. Frank Smith. The last three functions will be the focus of this paper, though the concerns to be discussed pertain to all six.

The essential functions of occupational health services

The essential functions of occupational health services come down to three pairs of things: prevention and protection, advice and guidance, treatment and rehabilitation. In an idealized and abstract form, these can be summarized as follows.

Prevention and protection: the occupational health service joins forces with a larger health system for prevention and protection aimed at the whole of the community against environmental and occupational disease. The occupational health service creates new knowledge and donates it to the knowledge pool, keeps up with the growth of knowledge in occupational health and in health generally, suggests from its experience the basis for new policy in prevention and protection, gains experience by carrying out surveillance through monitoring tests, monitors these tests' validity, sensitivity, and specificity, and their possible conflicts with human rights, correlates environmental and medical data, links work-related and non-work-related factors in the etiology of disease, safeguards privacy, and keeps medical and personal data confidential.

Advice and guidance: the occupational health service receives data from the developing corpus of scientific knowledge, and the occupational health service's own experience, uses the data to give information and advice to the clients of the occupational health service, and provides data to the corpus of scientific knowledge.

The occupational health service aims to provide those people in positions of responsibility with the information and advice which they need to make their decisions, whether they are employers, managers, trade unionists, workers, elected representatives, or government officials. The standards required for the information and advice are intelligibility, trustworthiness, and comprehensiveness; the process involves oral, written, and in recent times, electronic communication.

Treatment and rehabilitation: work is sometimes a treatment to disease, sometimes a cause of disease. There has to be frequent review so that those who need special care receive it, and so that treatment and rehabilitation are monitored for their effectiveness. There is a need to coordinate so that treatment, rehabilitation, and work cooperate in the individual's best interest, and so that a reasonable balance is struck between the individual's best interests and the interests of others, whether in matters of risk or finance.

Computers' essential functions relate surprisingly closely to the occupational health's essential functions, as can be seen from Table 1 which shows the relations in an abbreviated form -- there seems to be no part of occupational health for which the computer offers no function.

We need to begin by examining some general concerns about computers, and then look at some present and developing applications of computers in occupational health with an eye to seeing how real these concerns are.

Concerns about computers generally

People are concerned that computers destroy jobs, create uncertainty, spread insecurity because their records are raidable and destroyable, broadcast all our secrets, make huge errors, cost extravagantly, overwhelm, favour an elite, and promise the computer controlled depersonalized society. People wonder whether all the computerization is necessary.

It is true that computers destroy jobs, but data base building does require people; electronic communication is labour intensive, though high technology. It is true that computers instill insecurity to an alarming degree, but computer security is coming on apace, and vulnerabilities are reduced by duplication. It is true that computers occasionally make spectacularly silly mistakes, that computer fraud is a growing business, and that human vigilance is still required, but computers are increasingly sophisticated at detecting their own errors.

In response to such issues, the Government of Canada has proposed two computer related amendments to the Criminal Code: one would make it a crime to make unauthorized taps into a computer system, to intercept data, or to obtain computer services without authorization. The other would make it a criminal offence to destroy, alter, or interfere with the lawful use of computer data. In the end, the responsibility would remain with information handlers to protect documents in trust, but they would have a legal instrument to support them.

TABLE 1: Essential Functions of the Computer

1. Compile words, numbers
2. Link records
3. Process data from instruments
4. Retrieve information/data on-line
5. Communicate electronically
6. Educate

Essential functions of occupational medicine		Computers' essential functions
Prevention and protection	Donate and receive knowledge	4
	Keep up with growth in knowledge	4
	Create basis for new policy	4
	Keep up with policy	4
	Monitor by tests, monitor tests	12
	Correlate environmental/ medical data	123
	Link work-related/non-work related factors	123
	Safeguard privacy	12
	Maintain confidentiality	12
Advice and guidance	Donate and receive data	45
	Keep up with practice	4
Give advice and guidance which is	Intelligible	6
	Trustworthy	45
	Complete	4
	Assist a 'right to know'	123456
Treat and rehabilitate	Donate and receive 'shop' talk	124
	Search out interactions	12
	Review and coordinate	12
	Balance interests	5

It is true that computers are costly, but it is also true that cost of computers has declined, bringing personal computers, real computers, to the public for under a hundred dollars; even so, computers require careful budgeting just like any other valuable asset. It is true that computers are everywhere and that they can drown us in data, but it is also true that computers are the only way we have to manage the huge quantities of scientific information we need, often the only effective way we have of finding the information needle in the data haystack. It is true that computers could depersonalize society, but we live in the era of personal computers which are opening data bases for many people, even in their own homes. It is also true that computers are a promising approach to quality assurance in science, and a promising new way of publishing scientific information.

For the future, whether computers are unnecessary is a matter of perspective; for CCOHS, the way forward is unimaginable without them. For occupational health we see in particular two concerns pertaining to information and advice which we think should be addressed by the profession: the ethics of information and advice (who should know what about whom?) and the effectiveness of advice and guidance.

Who should know what about whom?

For some time, companies have been gathering personal and health data on their employees. Some of the information gathered takes the form of exposure levels of employees, obtained through personal and area monitoring devices, medical histories, and lifestyle information. These data can be correlated through a health management information system, permitting the company to be assured that no individual exceeds the accepted exposure limits, and assisting the occupational physician in monitoring the health of the individuals who make up the work force generally.

With personal and medical information in computer storage, security and integrity of the data should be a growing concern. Anonymity has to be maintained without making the data unavailable for legitimate purposes. Computers allow anonymity of data, though they do not guarantee it automatically. Specific data on exposure can be provided by computers without the identification of the individuals involved, by means of codes in the place of names so that the identities can only be discovered from a secure data base. But codes can be cracked, and data bases can be broken into. Secure data bases can be protected by passwords to the computer system, but passwords proliferate. These days, access to computer files is often possible from any location with a telephone. Security can be breached: the Sloan-Kettering Institute's experience is a reminder of how insecure computer systems can be.

According to the New York Times Service (1), some young men used a home computer to break into computer systems around the United States, including the computer held radiation therapy records of cancer patients at Memorial Sloan-Kettering Cancer Centre in Manhattan.

It seems that an Apple II computer was used for the tampering with the hospital's computer directory, and that access was gained through Telenet, a popular computer time sharing system used by more than 1,000 companies throughout the U.S.A.

Hospital officials were said to be almost certain none of the records had been altered and that no treatment had been affected, but they could not entirely rule out those possibilities. They had been aware of the tampering for some months, and had even left messages in the computer begging the culprits to stop.

According to the New York Times, the Sloan-Kettering Centre is one of the many institutions to be identified as a victim of computer tampering. Another is the U.S. Government's nuclear-weapons laboratory in Los Alamos, New Mexico (2). Suspected is a loosely knit group of young computer enthusiasts in Milwaukee, calling themselves the 414s, that city's telephone area code.

But breaching of security by tampering is by no means the only concern. Whilst many people accept the importance of storage of data for use by physicians, epidemiologists, toxicologists, and other researchers there is mounting public concern about the use of personal data on individuals. The challenge, yet to be resolved, is what does and does not constitute a legitimate purpose for the collection of personal data. The research community has to date assumed automatically a right of access; that assumption is now challenged, just as the right of researchers to experiment on hospital patients was challenged two decades ago, and just as the right of researchers to experiment on animals was challenged in the early part of the century. Codes of ethical practice served well in response to these earlier concerns; there is now a sore need for codes of ethical practice for epidemiological research, a job which the profession of occupational medicine might well take on. The key question is: what are the legitimate purposes for personal and health data collection? The answer, "for the sake of amassing data", is no longer adequate.

At CCOHS we have a data base listing the inquiries received by the Centre, which points to the files with the answers. This data base helps us avoid duplication of work, and provides access to one of the largest and, we feel, best researched collections of occupational health and safety topics. Yet our service could not function properly if we could not guarantee anonymity for our inquirers. We have to ensure that an inquirer can not be identified by the question that she/he asks, a significant risk where a question is highly specific to an industry or place. Inquirers' names are not entered into the data base and, as an additional protection, only CCOHS staff are permitted to access this data base. Of these staff, only those from the Inquiries Office are permitted to display all parts of the file. Other staff may access those parts of the data base concerned with their own inquiries or with the inquiries of individuals reporting to them. Data can be modified by no one other than the data entry staff in the Inquiries Office.

Effectiveness of advice and guidance

Occupational physicians, occupational health professionals, researchers, governments, employers, and labour have in common the basic need for information which meets the triple standard of trustworthiness, intelligibility, and comprehensiveness. This is a task, trivial enough at first, whose standards turn it into one of Herculean proportions, once you get involved.

The giving of information and advice according to these standards can be seen as an ethical duty of professionals at least equal in importance to everything else which is done professionally. The withholding of information was the allegation in a lawsuit, in the USA, involving information on the potential health effects of the chemical DBCP (1,2-dibromo-3-chloropropane), a pesticide developed by The Shell Company and Dow Chemical Company (3). Research had associated DBCP with impaired fertility in workers. The plaintiffs sued Shell and others for allegedly withholding information contained in a study, done in 1961 by the University of California, of the health hazards associated with DBCP. During the trial, Shell's evidence proved that the data were provided to the government on numerous occasions, as well as being published in a leading toxicological journal - demonstrating the legal importance of effective information systems. In some legal systems the employer's duty of care is to keep abreast of developing knowledge.

On the occupational health problems posed by vinyl chloride, the Science Council of Canada in 1977 commented (4):

> In the medical field, there is a need for better information exchange. The identification of the specific angiosarcoma of the liver attributable to vinyl chloride was greatly facilitated by the independent action of Dr. M. J. Phillips, Professor of Pathology at the University of Toronto, who had a particular interest in liver tumours. We have noted that the Department of National Health and Welfare took no steps to ensure that pathologists across the country were aware of this unusual tumour, and alerted

> to its possible cause and occurrence. We find it surprising that the Department of National Health and Welfare should be quick to take initiative in respect of food and drug problems and think it normal to send a letter to all practicing physicians in Canada concerning such matters, but should not have considered it to be within its normal sphere of responsibility to alert all pathologists about recently published information on a liver tumour attributable to a chemical substance that many Canadians were handling.

In reviewing the literature of vinyl chloride, one of us came to the uneasy feeling that the attack on the liver was foreshadowed in the scientific literature even before 1974 when Dr. Creech spotted the cases of angiosarcoma (5). A good information system could have made the world aware of this earlier. We would go so far as to say that failure to be aware of existing knowledge should be seen as inadequate professional performance. Is keeping abreast of developing knowledge not one of the prime reasons why occupational health professionals are employed? With the information systems now available, ignorance becomes less and less excusable.

While the trained professional mind is essential for linking unconnected data, computers can prove useful in this function too. An example is the way one of the inquiries received by CCOHS was answered about the hazards encountered by plumbers and pipefitters. These workers come into contact with welding fumes, so all publications dealing with the hazards of these fumes are relevant; these workers are exposed to other hazards such as asbestos, they experience back problems, and are subject to the various accident risks of the environment they happen to be plumbing and pipefitting. The computer allowed CCOHS staff to locate documents dealing with all these hazards as they relate specifically to plumbers and pipefitters, and to exclude those which were not relevant because they related to other occupations. The documentation would have been too large to handle otherwise.

At risk of laboring the point, we repeat that the computer is of special help not only in storing bibliographical information (including abstracts), but also in providing near-instant retrieval. As an example, searching a large data base such as Chemical Abstracts, is actually simultaneously 'browsing' as many as 12,000 scientific journals. Table 2 illustrates the scale of the information pool, by showing the large number of documents published on certain topics common in occupational health and safety.

The data bases mentioned in Table 2 are a sample of those available to the occupational health community, on a somewhat limited and expensive basis, from commercial data base vendors.

TABLE 2: Data Base Survey: Ten Occupational Topics Covered in the Scientific Literature, From 1975 to 1981

Data Base Originator	Approximate Total Number of Citations in Complete Data Base	Occupational Topic	Total Number of Citations
CIS d'informations de sécurité et d'hygiène du travail (of the ILO) Geneva, Switzerland	16,000 bilingual English & French records 1969 - 1981	noise	840
		asbestos	358
		vibration	357
		microwaves	29
		chromium	113
		back problems	60
		dermatitis	29
		pneumoconiosis	130
		benzene	129
MEDLINE U.S. National Library of Medicine Bethesda, Maryland	3,500,000 1966 - 1981	stress	2,395
		noise	979
		asbestos	688
		vibration	488
		microwaves	107
		chromium	275
		back problems	1,219
		dermatitis	1,183
		pneumoconiosis	496
		benzene	269
EXCERPTA MEDICA Excerpta Medica Amsterdam, The Netherlands	1,280,000 1974 - 1981	stress	4,863
		noise	2,822
		asbestos	1,228
		vibration	1,421
		microwaves	282
		chromium	853
		back problems	5,407
		dermatitis	1,086
		pneumoconiosis	2,651
		benzene	824

TABLE 2 (continued)

BIOSIS PREVIEWS BioSciences Information Service, Philadelphia, USA	3,087,000 1969 - 1981	stress	1,743
		noise	761
		asbestos	854
		vibration	425
		microwaves	113
		chromium	698
		back problems	922
		dermatitis	351
		pneumoconiosis	328
		benzene	1,005
SAFETY SCIENCE ABSTRACTS Cambridge Scientific Abstracts, Inc. Oxford, England	100,000 1975 - 1981	stress	303
		noise	563
		asbestos	153
		vibration	202
		microwaves	53
		chromium	64
		back problems	175
		dermatitis	44
		pneumoconiosis	79
		benzene	78
NIOSHTIC National Institute for Occupational Health and Safety Cincinnati, Ohio	Records 80,000 1974 - 1982	stress	1,891
		noise	2,257
		asbestos	1,124
		vibration	682
		microwaves	399
		chromium	411
		back problems	85
		dermatitis	787
		pneumoconiosis	673
		benzene	476
INFODOC Canadian Centre for Occupational Health and Safety Hamilton, Ontario	12,000 1982 - 1983 (Canadian - English & French/ language material, inter-structural material)	stress	171
		noise	304
		asbestos	321
		vibration	49
		microwaves	57
		chromium	66
		back problems	36
		dermatitis	52
		pneumoconiosis	48
		benzene	37

The smaller companies, the smaller occupational health services, worksite occupational health and safety committees, labour unions, and the smaller departments of government have been able to take only limited advantage, if any, of these essential services. Recognizing that problem, and in order to facilitate the dissemination of bibliographical data in occupational health and safety, CCOHS mounted on a Hewlett-Packard 3000 computer the NIOSHTIC and CIS data bases, plus several of its own data bases. These services are now available to our users, according to prevailing CCOHS policies, for merely the costs of data transmission, terminal maintenance, and training. The training is given by personnel from CCOHS well acquainted with the information needs of the occupational health community, because of the extensive experience covering four years, of our human based information and advisory service.

Because Canadian material is often ignored in the larger American and European data bases, one function needed of CCOHS is to record all that has been written on occupational health and safety in Canada. In response to this problem, CCOHS is creating a data base known as INFODOC, an index to documents held by CCOHS. We see increasing opportunities for exchanging access to national files with other countries.

One of the strengths which is at the same time one of the weaknesses of bibliographic data bases is that they often do not give the actual information required, but merely act as a catalogue for it. Without ready access to good library facilities, the usefulness of these data bases might be limited. Much of the material found in a bibliographical data base is of a specialized and technical nature -- fine for the researcher or specialist, but not necessarily suitable for the average manager, worker, or government official. In order to overcome these limitations, CCOHS is exploring videotex, another use of computers for information dissemination in occupational health.

As a first step, CCOHS has developed prototype data bases on asbestos and construction safety, using the Canadian videotex system, Telidon, a world standard setter in the field. CCOHS is influenced by the experience of the Health and Safety Executive in the United Kingdom which has already begun on-line uses of videotex in occupational health; we do not see videotex supplanting the bibliographical data bases so much as supplementing them.

Videotex systems have the capacity for storing graphics, and for animation. Soon they will have voice capabilities as well. Videotex could do for computer information systems what the animated cartoon did for the movies as an instructional medium in the 1930s and 40s, but with the differences that the user can search the information in the computer and the computer can quiz the user. Videotex is not difficult to use and requires no previous training of the user, a significant advantage over the bibliographical data base, which is and does.

The information in videotex and, indeed, all data bases can be layered: data can be stored and accessed in layers corresponding to various levels of user expertise in occupational health and safety (Table 3). A user is presented with a menu from which she/he selects what is needed; if already familiar with the topic, she/he can skip the introductory layers. Information layering requires careful study of the information needs of users and patterns of use of our system.

Layering of information and, indeed, all information and advisory work is futile if the information is untrustworthy. We see two chief concerns over trustworthiness, which the computer might help us deal with: (a) uncertainty and (b) defective information. Uncertainty presents a challenge not only to occupational health, but also to science in general. A conventional view of the growth of scientific knowledge has been that, like bricks, items of knowledge are built one upon the other, so creating a solid scientific structure built on solid scientific foundations. This may well be what happens, but there is another equally important parallel activity: constant movement from certainty to uncertainty. The early Church was certain in its knowledge of the Heavens; the mathematicians and astronomers made the Church's explanations uncertain.

TABLE 3: Layered Approach to Information Dissemination

Depth of Informational Required				
layer 1	layer 2	layer 3	layer 4	layer 5
Basic information in simple language consisting of illustrations where necessary	Direct technical information eg. Hazard Summary Series	Direct technical information on specific topics providing an indepth analysis of the subject matter. Special reports and publications	Bibliographic information enabling the user to identify and study relevant documentation on the subject	Analysis and interpretation by CCOHS scientists

Einstein made Newton's knowledge uncertain and, doubtless, scientists are still hard at work creating uncertainty out of Einstein's work. In occupational health, we have only to think of the way in which ideas are changing about non-ionizing radiation, occupational carcinogenesis, and medical surveillance to recognize that the march of scientific knowledge exposes us to widening horizons of uncertainty. There are many things we understand clearly now which we will be uncertain about in the future. Occupational health is full of uncertainties; research is increasing their number and scope. Occupational health needs to learn to cope with uncertainty, in its scientific implications, in its social implications, and in its professional implications.

Decisions in occupational health have to be made after a weighing of all the available evidence. Computers may be able to help identify the evidence in the first place, and they may be able to assist us in other ways, if occupational health can first develop means for approaching uncertainty. We have nothing to propose at this time, we say simply that uncertainty represents a problem in need of attention in occupational health.

In the continuing struggle of science with uncertainty, individual scientists have not always dealt fairly with the uncertainties of their own data. From the book Betrayers of the Truth (6), we can see evidence that Claudius Ptolemy, Galileo Galilei, Isaac Newton, John Dalton, Gregor Mendel, and Robert Millikan fudged their data. The IBT scandal, resulting in a trial in Chicago during 1983, may add an occupational health example to the list of infamy in science. This scandal led, in Canada at least, to a first in occupational health: a recall on scientific data put out by the most respected government scientific authority in Canada, the National Research Council. We are accustomed to recalls in the automobile industry, but not on scientific data pertaining to pesticides.

Downright fraud is mercifully rare in occupational health, but most of us would accept that there are defects in scientific information in occupational health: inadequacies, incompleteness, bias, shoddiness. All of us in reviewing the literature on a particular topic in which we are knowledgeable must at some time have had the experience of wondering whether we had covered all the important and relevant material (we are uncertain of our own knowledge; we were uncertain of the state of knowledge generally on the topic). As we come to know a topic well, we recognize gaps in other people's treatment of it; we come to see defects in the scientific information on specific topics.

The demand for trustworthy, intelligible, and comprehensive information and advice appears insatiable: if the experience of CCOHS is anything to go by, this is the fastest growing area in occupational health and safety. Inquiries received by CCOHS are doubling in number each year, and our capacity to handle them on a one-to-one basis is declining. Without the use of the computer, an untenable situation would develop in the near future. CCOHS must use computers to disseminate and publish information electronically. This process is not radical in that in North America, at least, there are cable television channels which broadcast streams of the latest news to home viewers through channels dedicated to this purpose.

CCOHS publishes much of its own material by electronic transmission between the word processors and the printing company. The Chemical Hazards Summary (#1 Methyl Ethyl Ketone), was produced by CCOHS in this way. By appearance, this seems nothing out of the ordinary, merely a five-page, double-sided document with a one-page summary, printed in large, clear type on inexpensive paper. It is different from most other publications in occupational health and safety because of the extent to which computers are involved: it is essentially electronic; paper is merely one of several possible forms in which it can appear. Others are as hard copy printout from a terminal connected to a computer based system, as text on the screen of a VDT connected to a bibliographical data base system, as text on the screen of a videotex system. For the printed paper version, the type was set electronically by adding typesetting commands to the original electronic text, begun with scientists dictating into a microphone. A human operator is still required for transposing the sound of the scientists' voices to the electronic record, but the future appears to hold voice recognition systems so that this part of the process may also be taken over by microcomputers instead of human word processors, as at present.

The scientists compiling the summary relied on data bases and other computer facilities for acquiring, sifting, and evaluating the information which the summary is based on. These and other data bases point the way to the further information which is available should someone's needs not be satisfied by the summary. In the future, data bases will have reached the point where you can have one stop shopping and get everything you want to know on one topic out of them.

In this regard, CCOHS is on the way already, because Chemical Hazards Summary #1 is a building block for a data base which, through the Chemical Abstracts Registry Number, links with a whole family of data bases, some held by CCOHS. With such links, an inquirer can reach the chemical summary even if he or she is aware only of the trade name of the chemical (as used in Canada, that is), because through another of our own data bases, CHEMINFO, the trade name can be linked with the Chemical Abstract Registry Number. Chemical Hazard Summary forms part of the chemical information system which CCOHS now has on-line. With this as the starting point, someone could search much of the existing scientific knowledge on methyl ethyl ketone, originally published in several languages. Through videotex, we will be able to show diagrams of the structural formula or any graphs, drawings, and animated diagrams which would be helpful in communicating the information itself or the understanding of it. Another application would have videotex convey the blueprints of the control technology.

The elements of the Chemical Hazards Summary were defined by our understanding of our clients' needs, an understanding gained through the experience of handling nearly 10,000 inquiries from workers, management, and government on virtually the entire spectrum of occupational health and safety. That there exists a need at all for hazards summaries might be surprising, given the huge amount of effort which has been put into occupational health and safety in North America alone. But our clients made it clear to us, occasionally in a pointed way, that their needs were not being met by existing means, and that they were looking to CCOHS for the help they could not get elsewhere. Our understanding of their needs enabled us to define the elements of the summary. Whilst these might not at first glance appear all that different from existing documentation, such as the NIOSH criteria documents, material hazard data sheets produced by chemical corporations, and the ACGIH TLV List, a side-by-side comparison shows that the CCOHS documentation represents a new and different balance of elements, a balance which represents a deliberate attempt to serve a defined user group whose information needs have been understood, to serve them with trustworthy, intelligible, and reasonably comprehensive information.

The computerized system utilized by CCOHS is designed so that persons accessing it can request specific information. At present, much of the information held by CCOHS in its computerized system consists of retrievable bibliographic data plus summaries of occupational health and safety documents. Data bases under development supply information on chemical products and pure chemicals. These are already available on an experimental basis and they are planned to be available soon to a wider user public.

The system we are planning will have a network of users of our computerized information service. Our idea is to link people and let them tell us not only what they want in the way of information and advice, but also what they know about the solutions to problems in occupational health and safety. An electronic mail system would do this, by which persons could send messages to CCOHS and by which the staff of CCOHS could reply. With a message forwarding capability, messages received by CCOHS can be sent to others who might be interested. An electronic mail system would allow people to comment on information published by CCOHS or received by CCOHS from other persons using the system: people could stake out all points of views on a dichotomy and clarify an issue. If our network were set up on these lines -- and it could be -- we would expect communities to form around issues like the hazards of visual display terminals, medical surveillance, the differential dangers of asbestos, and a host of other controversies in occupational health and safety.

Notice that we began by talking about an electronic mail system and suddenly we are publishers. Two-way communication channels are very powerful systems.

One such network, the Electronic Information Exchange System (EIES), is already in operation (7). People are using its electronic mail and conferencing system to find consultants to hire, to discuss a job-related problem in a neutral environment, to take a devil's advocate position in a 'discussion' while retaining their anonymity through the use of a pseudonym, to celebrate a special occasion with others in their electronic community, and to publish 'articles' on the topic of mental workload (a formal publication of EIES).

Two other electronic publishing systems, The Source (owned by Readers Digest) and CompuServe (owned by H&R Block) discovered that people sign up to use their systems for one reason but usually use it for another. Many people contract with The Source because it has available an electronic news service, but the most heavily utilized parts of the system involve people communicating with each other. It remains unclear why people want to communicate with each other in this way, but there is reason to think that if -- perhaps it should be when -- CCOHS introduced such a service it would be heavily utilized by those in the occupational health and safety community.

CompuServe allows subscribers to create publications which others can utilize, and it pays a royalty to the information provider, based on usage. Users of these information services often know, through self-examination, what others want and, to a certain extent, need; they can often provide this information where no one else can.

The possibilities for a two-way system seem endless and unpredictable. For example, Qube, a cable company in Columbus, Ohio, used a two-way cable system with a numeric keypad used to send one or more numbers to the cable TV company's computer. During a specially arranged football game, the audience watching the game on television was asked to decide which plays the home team should attempt. The audience was given a few plays to choose from (one of which was "coach's choice"), identified by a number. The computer polled all the connected keypads and gave the pooled selection to the coach for implementation. Perhaps the home team would have lost anyway!

The moral of this story is that two-way communication systems are not in themselves sufficient. There has to be an experienced and knowledgeable authority in the information providing process. For two-way occupational health, we see CCOHS as the authority.

It is regrettably true that the trustworthiness of scientific information is judged in part by the authority of the author of the information. CCOHS has made a conscious effort to establish itself as an authority, as a source of trustworthy information. The tripartitism of the governance of CCOHS has been a major factor in achieving the existing degree of acceptance among the three parties: government, management, and labour. We have objective evidence of that acceptance through an independent study of user response to our service, a study which showed a high degree of satisfaction among all three parties. Tripartitism provides the environment of trustworthiness because it protects science against manipulation by any one interest group; the ultimate test is the quality of the scientific information.

CCOHS operates an increasingly effective system of quality assurance, in which computers will play more and more of a part in the future, a part aimed at ensuring that the information we present is neither partisan, nor partial, nor imprecise. The references at the end of the Hazard Summary show the evidence upon which we are relying primarily; in selecting that evidence we have relied heavily on computer systems. We are as sure as it is possible to be of the present state of relevant western scientific information, and we are sure that we have introduced no distortion through our selection of information upon which we relied for the summary. Regrettably, we cannot yet say that about scientific information from the Eastern bloc, because so little of it is in the data bases we access; with the exchange arrangements we are increasingly developing we hope soon to remedy such gaps.

About trustworthiness generally are three points which the occupational health and safety community ought in our opinion to be considering carefully:

1. that scientific information is no longer automatically assumed objective and credible merely because it appears scientific;

2. that the organization from which information and advice comes has itself to be seen as trustworthy; for whatever reason, information and advice coming from government, corporations, and labour unions is not to be automatically trusted and should be regarded with caution concerning partiality, partisanship, or even bias; and

3. without computer systems, the handling of uncertainty of knowledge about occupational health and safety becomes an unmanageable task for all professionals in occupational

health and safety, and most researchers -- yet management of uncertainty is arguably the most important function of information providing and advice giving which, in turn, are arguably the most important professional functions for the next decade of occupational health practice.

Predictions and other divinations

CCOHS would like to provide the optimum system to meet the information needs of the occupational health and safety community in Canada. We need to know who will be using the system in the future and how it will be used; predictions are an uncertain business. In 1978, British Telecom estimated that there would be 1 million users of Prestel, the British videotex service, by the end of 1981, most of whom would be accessing the system from their home. At the end of 1981, Prestel had 15,000 subscribers, of which 14,000 were from the business community.

With this experience of predicting the future in mind, CCOHS is prognosticating that its proposed videotex service of occupational health and safety information would be utilized mainly by joint occuaptional health and safety committees (it is estimated that there are 20,000 such committees in Canada), for which the educational potential of videotex seems especially promising.

With the domestic television used to access movies on pay TV; other cable channels; news, weather and sports; home shopping and banking; games, home-made video movies, cassette and videodisc movies; computer programmes; and electronic mail systems, not to speak of blue movies, who will dial into the CCOHS system for information on asbestos? If even a small percentage of the population did, CCOHS would be serving a large number of people (if 0.1% of the Canadian population dialed into the CCOHS information system once a year, there would be 2,000 people accessing the system each month). The unknown here is the motivation and interest which result when a person perceives that his or her life or health is threatened by something encountered at work. If the experience of our non-computerized system is anything to go by, there could be a significant demand, especially when account is taken of the discovery by CCOHS that an average of 20 people see and use each response sent out by CCOHS in response to each inquiry.

CCOHS is placed in the interesting position where it has to do more than develop an expertise in occupational health and safety; more information must be obtained about the behaviour of users of computerized information systems. The Source found that users of their system frequently began naive, but became sophisticated within six months. One executive of a software company stated that some users of their software know more about its capabilities and limitations than the company. The design of an information system must take this learning factor into consideration, and be flexible enough to allow the redesign of the system as the users' experience grows.

To the problem of training people for work, industry has found part of the answer, an answer tied to the software revolution, an answer which foreshadows things to come. Some corporations have consciously decided, apparently, to direct their resources into training computers, not people: resources are being directed to software development. Software can propagate faster than people can be trained; software has the capability of interacting with other software and of benefiting from the experience. Computers learning from each other is the stuff of science fiction, now reality and a somewhat frightening industrial revolution.

There is an increasing proliferation in the workplace of robotics, machines which are controlled by computer technologies. There are predictions that 315,000 industrial robots will be in use in North America by 1995 (8); it is estimated that 5,000 high-performance industrial robots ('defined as a programable, multi-function device designed to manipulate and transport parts and tools and do specialized manufacturing') (9) are now in use in the United States. Workers will be working increasingly with, and beside these machines. We hope that the dangerous work will be carried out by the robots and not the people.

All this seems to show where industry should place its resources to decrease accidents: in the development of software for robots, not hard hats for workers; in training computers how to perform workers' functions more safely. It is said that three years are required to train a human in the skills needed on an assembly line compared with 20 minutes for a robot with its computer memory (10).

It is no wonder that people fear for their jobs, especially as data base building and electronic communication do not seem to be opening up new jobs at a similar pace.

And yet, in all the newness lurk the old dangers. You may have seen the spectacular court awards in the USA resulting from a robot seriously injuring a worker. Stripped of its technological mystery, this accident goes back to the very beginnings of the industrial revolution, when workers were being killed by the new textile machinery because it was not securely fenced. In assimilating the new technology we cannot afford to forget the old lessons in occupational health and safety, any more than we can dodge the issues with which the computer confronts society, as a whole, as well as occupational health and safety.

The opportunities presented to occupational health by computers combine with concerns about computers generally. Anxieties about computer applications in occupational health give some important responsibilities to the occupational health and safety community. In our opinion, this community has the responsibility to:

1. understand the concerns people have about computers generally and specifically about data in trust, that is data of a personal nature held by computers;
2. define and get wide social agreement on the legitimate purposes of personal data in regard to epidemiology and other types of investigation;
3. establish and maintain standards of custodianship;
4. inform reliably, fully, and intelligibly in matters of occupational health and safety; and
5. define and get wide social agreement on what is and is not confidential not only in regard to personal data, but also in regard to chemical and other technical information.

The first three of these responsibilities pertain to data in trust; the last two, to trust in data.

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COMPUTERS AND INFORMATION NEEDS IN OCCUPATIONAL MEDICINE

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Today I will concentrate on three concepts in reviewing Medical Needs in Occupational Health: data, information, and validation. The process of collecting data, transforming data into information, then validating the information is not trivial: it has transformed medicine from a 19th century 'art' to a 20th century science.

I'd like to begin by examining the transformation of medicine which began more than a century ago, concentrating on the concepts of data, information and validation in order to explore and illustrate the profound power of the process to transform. As we consider the evolution of medicine in the present century I will look at specific examples of what physicians thought they knew and examine how they learned what they really know. In other words, how their information was validated. I will relate medicine to occupational medicine, then illustrate data, information and validation by considering a specific computer system, Exxon's Health Information System (1,2). Finally, I will make some suggestions about a systematic approach to information needs in occupational medicine aiming at how best to use this technology in our chemical industry medical departments.

Environment is not a 20th century concept either in medicine or in occupational medicine. In the 19th century classical medicine considered the human body as a system of dynamic interactions with the environment (3). Health or disease was a consequence of cumulative interaction between constitutional and environmental circumstance. One's body was constantly adjusting to climate or circumstance, balance was all important; imbalance produced ill-health. Therapies for disease aimed at 'regulating the secretions': extracting blood , promoting perspiration, urination or defecation in order to regain the equilibrium which determined health. Physicians in 1800 had only their senses for diagnostic tools. Pharmacology or materia medica dealt with categories of physiological effects: diuretics, cathartics, narcotics, emetics, and diaphoretics. The physician 'worked' by providing predictable and visible effects.

During the 1830's, a new concept appeared: the natural history of disease. The School of Paris was particularly effective in marrying clinical observation of living patients with the new discipline of autopsy pathology in order to develop data and make correlations. Data became information. Disease was regarded as more complex than an imbalance between constitution and environment. Diseases were recognised as distinct entities with characteristic cause, course and symptomatology. The appreciation of certain processes as being self-limited stayed the enthusiasm for rigid, doctrinaire therapies which often did more harm than good. The transition was not smooth, however, and an indignant New York physician complained in 1836 that the French were... "tearing down the temple of medicine to lay its foundations anew... they lose more in their Therapeutics than they gain by morbid anatomy - They are explaining how men die but not how to cure them." (4)

A second set of powerful influences on medicine in the late 19th century came from the universities and hospitals in Germany where laboratory and investigative medicine developed and flourished. Chemistry and physiology, and perhaps most influentual of all, microbiology, began to generate experimental data which in turn was transformed into clinical information. French pathology and German 'bench-bedside' science acted synergistically to initiate a profound transformation of medicine. Thus by the turn of the century the 'causal' theory of disease was in its ascendency.

In North America, a Canadian, William Osler, emerged as the most influential educator and physician. A prominent aphorism of Osler (later knighted by the British) is shown on the first slide: "Patients don't die of their disease, they die of the physiological abnormalities of their disease." (5).

Lewis Thomas in his delightful autobiography, The Youngest Science - Notes of a Medicine Watcher, provides a glimpse of this Oslerian tradition:

> "The medicine we were trained to practice was essentially Osler's medicine. Our task for the future was to be diagnosis and explanation. Explanation was the real business of medicine. What the ill patient and his family wanted most was to know the name of the illness, and then, if possible, what had caused it, and finally, most important of all, how it was likely to turn out.
>
> The successes possible in diagnosis and prognosis were regarded as the triumph of medical science, and so they were. It had taken long decades of careful, painstaking observation of many patients; the publication of countless papers describing the detailed aspects of one clinical syndrome after

> another; more science, in the correlation of the clinical features of disease with the gross and microscopic abnormalities, contributed by several generations of pathologists. By the 1930's we thought we knew as much as could ever be known about the dominant clinical problems of the time: syphilis, tuberculosis, lobar pneumonia, typhoid, rheumatic fever, erysipelas, poliomyelitis. Most of the known varieties of cancer had been meticulously classified, and estimates of the duration of life could be made with some accuracy. The electrocardiogram had arrived, adding to the fair precision already possible in the diagnosis of heart disease. Neurology possessed methods for the localization of disease processes anywhere in the nervous system. When we had learned all that, we were ready for our M.D. degrees, and it was expected that we would find out about the actual day-to-day management of illness during our internship and residency years."(6).

Thomas speaks of data then, and information. But what of validation, the third concept I promised to consider? Did physicians really know what they thought they knew? Validation is the process by which we test information. Validation aims at the essential question: can information or technology be counted on to perform predictably in a certain set of definable circumstances?

Let's use Walsh McDermott's example of testing for syphilis to illustrate validation (7). Wasserman introduced a serological diagnostic test for syphilis early in the century which was exquisite in its sensitivity: few patients with untreated active disease had negative reactions. The test was widely used but only after four to five decades did the fact emerge that the Wasserman test was oversensitive. Of those people with positive reactions, only about half were actually syphilitic. Apart from the mental anguish brought on by a diagnosis of syphilis, thousands of people were subjected to an arsphenamine derivative which also carried substantial risk of producing hepatitis. Thus while the diagnostic test was powerful and most useful in the diagnosis of active spirochete infection, the lack of validation prior to application produced harm as well as benefit.

Let's consider another example of the importance of validation in clinical medicine and use a more recent bench mark, the study of pneumococcal bacteria and pneumonia by Austrian and Gold (8). Twenty years ago overall mortality was an impressive 24.8%. Since then, physicians treating such patients have had a variety of new technologies: new antibiotics, reliable and easy to use mechanical ventilators, pharmacologic vasopressor therapy, renal dialysis, electronic monitoring of cardiac rhythms, and finally, new antiarrhythmic agents. Recalling Osler's aphorism, we as modern physicians seem much better equipped to favorably control the physiological abnormalities of pneumococcal disease. Yet in 1974 mortality in a series of patients with pneumococcal bacteria and pneumonia reported by Mufson, et al. was 28% (9), and in 1983, by Hook, et al. it was reported at 31%. Factors influencing outcome appear to be leukopenia, age, and the presence of chronic illness.

A final example from clinical medicine is that of death from esophageal bleeding in patients with alcoholic cirrhosis. When I was in training as a house officer during the 1960's portacaval shunt surgery to decompress the distended esophageal veins was the mainstay of our intervention. Surgery was effective in preventing death from upper gastrointestinal bleeding. Years later when data became information and information was validated, we discovered we were simply substituting hepatic encephalopathy for variceal bleeding. In the important validation study by the Boston Inter City Liver Study, over the eight years following intervention, no difference in outcome was apparent comparing patients after surgery with controls (11).

Thus far I have limited my examples to clinical rather than occupational medicine for several reasons. First to show the fundamental importance of data, information and validation in medicine in general, and secondly, because the context becomes even more complex in occupational medicine where influences are multifactorial. Futhermore, the amounts of data required for us to practice our discipline are overpowering.

As physicians in the chemical industry with workplace and ambient environments as our 'hospital or laboratory' we must become comfortable and adept at using the new technology available to us. Look at the way in which public health as a discipline has been rejuvenated. Data, information and validation have identified 'new' diseases: Legionaires Disease, Acquired Immunodeficiency Syndrome, Burkitt's Lymphoma, and Human T-Cell Leukemia come prominently to mind.

As we consider infectious disease surveillance as a model for our own surveillance systems in the chemical industry, let's look more carefully at the factors involved. The following summary, taken from Thacker, et al., define the process of surveillance with a series of nouns: collection, collation, analysis, dissemination and finally, action (12). The systems essential to surveillance are complex and identifiable in this context only to suggest that we need to look carefully in order to decide their value to us in occupational medicine in the chemical industry.

Let us now consider one example of how modern systems technology is being used in occupational medicine in the chemical industry to capture data and effect the transition to information.

Our major objectives in developing our Health Information System, or as I will abbreviate, HIS are: first, to collect data, transform data into information on employee health and occupational exposure necessary to assure a healthy work environment; second, to improve the effectiveness of medicine and environmental health departments; third, to provide the information necessary to shape programs protecting the workplace and the ambient environment; fourth, to provide timely response in demonstrating compliance; finally, and most important in the practical sense, to establish a continuous data base for health and exposure information driven by daily routine operations.

There are five component modules of HIS. Substance Monitoring provides information on 'what, where, when, how much' and is a major component of the industrial hygiene portion of the system. The second critical portion of the industrial hygiene portion is Employee Tracking, a module which provides information on 'who, where, when'. Employee Tracking is derived from the payroll data at individual plants and is a prominent example of how useful information can be moved from one system to another. Both substance Monitoring and Employee Tracking are integrated into the Medical Surveillance module which permits the physician to access the data, schedule exams based on exposure information as will as to collect and analyze data. Reporting and Epidemiology are the remaining modules.

Our system is designed around distributed mini-computers. We have a dedicated Hewlett-Packard 3000 computer in the company medical department in Houston which supports six operating sites with 4400 employees for Exxon Chemical Americas and four sites with 7000 employees for our refining affiliate in the U.S.. The medical activities in the metropolitan NY area are supported by a second HP-3000 tracking two sites, 3400 employees, for our engineering organization as well as two sites, 4000 employees, based in New York City and at our Exxon Biomedical Science Laboratory in rural New Jersey. The 'Core' development support comes from our central systems installation in New Jersey with local installation support and maintenance being provided by our Houston systems group.

Overview and priority setting are provided by a central Steering Committee which acts as the client for the several systems groups involved with continuing development and maintenance of the project. The specific services provided for the 'Core' of HIS include technology upgrades, enhancement or improvement in capability, and of great importance, documentation of what is being modified. The installation support services include user training, telecommunications support, local interface issues and local or 'Non-Core' improvements.

One essential but somewhat troublesome area for us as physicians and professionals in the chemical industry involves project costs. In developing HIS, we found that phasing or staging the project helped us to control expenses and actually 'deliver' on time and within budget. Our maximum effort and expenses in 1979 were devoted to writing specifications and with early development work limited to the modules supporting industrial hygiene. During the second year of the project, 79% of our effort went into industrial hygiene, but by 1981 the effort was balanced between industrial hygiene, medical surveillance and reporting. By 1982, total costs of development were decreasing with efforts and costs limited to medical surveillance and reporting.

Systems costs in some ways remind me of bacteria in proper media with optimum temperature - growth is exponential. It is essential that you consider support and maintenance costs when you plan with your organizations what resources you'll need. Our support and maintenance costs have changed in distribution during the last three years. As percent of maximum annual cost, in each of the years, computer or hardware costs are the least of the four categories of expenditure. As development decreased, we spent less on system analyst time. As HIS came online in the operating companies, telecommunication costs have risen. As our users gain more experience they have defined problems and anticipated new needs - thus our costs for enhancement or improvement continue to be a major part of our budget.

I'd like to step back from the specific example of an occupational medical system for a moment and share with you some lessons we've learned in the years we've been involved with HIS.

When you talk with your own systems people and with vendors selling 'systems' to meet your every need, there are nine considerations I'd suggest that you keep in mind. Capital and operating costs, responsiveness, flexibility, security, development time and cost, and finally, maintenance time and cost.

As we moved into this area of information technology we found it essential to see that the system was well-integrated into our medical organizations. The four tenets we found useful were:

Know clearly what you want
Be certain that your resources are balanced
Focus clearly on the incentives for users
Be clear about costs and benefits.

In committing yourself and your organization to a major systems project such as HIS it is essential that you do not underestimate what is necessary for you as the user or client to provide. At each major stage in project development, application of the idea, scoping, exploration, user design, systems design, development, start up and operation, significant input is required from the medical department. The consequences of inadequate involvement are profound: you will not end up with what you need, the waste of money and resources will be significant, and you will lose credibility with your management.

In summary, data, information and validation describe a process fundamental to the transformation of Western medicine since 1800. Hardware and software technology greatly increase the potential for change, and because of the nature of occupational medicine, are particularly important for as in the chemical industry. In Exxon with our HIS system we are doing well with collecting data, beginning the process of developing information but have yet to get to validation. Our goal is to make our system 'evergreen': flexible, responsive, cost-effective, and as useful to us in occupational medicine as stethoscopes are to the cardiologists.

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INTEGRATED COMPUTERIZED COLLECTION IN OCCUPATIONAL MEDICAL, AMBIENT AND BIOLOGICAL MONITORING DATA IN THE CHEMICAL INDUSTRY

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Abstract

The large number of separate data in industrial medicine and hygiene leads to the need for their computerized storage and evaluation. Our program elaborated for this has taken into consideration the German legislation concerning industrial hygiene as well as the company's peculiar requirements. This report deals with our experience using the computer in the occupational medical care of about 50,000 employees in the chemical industry under the following aspects: rationalization of procedure in the medical department for several hundred persons daily; storage of the past occupational history with a constantly updated record for each employee by type and extent of exposure; documentation of diagnoses, laboratory and biological monitoring data; registration of causes of death and cases of cancer under occupational medical criteria; availability of these data for epidemiological studies; constant updating of accidents and intoxications.

In the Federal Republic of Germany air monitoring particularly for carcinogens falls under the rules of obligatory measurements. These include the definition of work areas, special modes of evaluation, the registration of the exposed employees, their exposure times, the preservation of data as well as the notification to the trade insurance. Using the same identity number these exposure and medical data can contribute to a quantitative risk assessment.

Applying the IBM 8100 system the problems of data security and professional secrecy have been given special attention. Personal experiences of a two year use of the program are compared with systems developed elsewhere particularly in the US.

Résumé

La grande quantité de données distinctes en médecine et hygiène industrielle nécessite une évaluation et un stockage informatisés. Notre programme qui répond à ce besoin tient compte de la législation allemande sur l'hygiène industrielle ainsi que des exigences particulières de la compagnie. Le présent rapport traite de l'expérience comportant l'utilisation d'un ordinateur dans le programme de soins médicaux pour

maladies professionnelles, offert à 50,000 employés de l'industrie chimique. Les secteurs informatisés du programme sont: la rationalisation du protocole dans le service médical consulté par plusieurs centaines de personnes quotidiennement; le stockage des antécédents d'emploi et la mise à jour du dossier de chaque employé selon le type et l'importance de l'exposition; la documentation des diagnostics, les données de laboratoire et de contrôle biologique; l'enregistrement des causes de décès et des cas de cancer selon les critères médicaux de santé professionnelle; la disponibilité de ces données pour les études épidémiologiques; la mise à jour constante des accidents et des intoxications.

Dans la République fédérale d'Allemagne, le contrôle de la qualité de l'air, particulièrement en regard des carcinogènes, est régi par le règlements sur les mesures obligatoires. Ces règlements définissent les lieux de travail, établissent des méthodes spéciales d'évaluation, et incluent l'enregistrement des employés exposés, la durée de l'exposition, le stockage des données de même que la déclaration à l'assurance du corps de métier. En utilisant le même numéro d'identification, les données médicales et d'exposition peuvent faciliter une évaluation quantitative du risque.

Lors de l'utilisation du système IBM 8100, les problèmes de sécurité des données et de secret professionnel ont fait l'objet d'une attention spéciale. Des expériences personnelles d'une utilisation du programme pendant deux ans sont comparées avec celles de systèmes mis au point ailleurs et particulièrement aux Etats-Unis.

Introduction

Few of the computer programs developed for medical tasks can be readily used for occupational medicine. Surveillance programs undertaken in occupational medicine and industrial hygiene generate a mass of individual data. If these are to be evaluated conventionally, a costly editing process is required, due to the virtually unlimited permutations of mutually interacting factors. Regulations covering occupational medical check-ups, obligatory recording of measurements and their storage vary from one country to another. In designing a computer program for occupational medicine and monitoring it is necessary to allow for these regulations as well as for factors specific to the company in question, particularly its production, size and geographical location.

Our report is based on experience of using a computer program, Bayer Computer Program Medicine - Monitoring (BCPMM), developed by ourselves, to assist with the provision of occupational medical care and measurement-based supervision of workplace hygiene of the about 50,000 Bayer AG personnel employed at the Leverkusen, Wuppertal and Brunsbuttel factories.

Terms of Reference

The objectives in view are as follows:

A. Occupational Medicine:

1. Streamlining of the procedure for carrying out several hundred examinations or treatments per day, and documenting the findings.
2. Documentation of laboratory data.
3. Compilation of the past occupational history, and of an exposure record.
4. Documentation of clinical diagnoses, including cases of tumours.
5. Statistical record of causes of death under occupational medicine and of job-specific aspects.
6. Data collection for epidemiological studies.

B. Monitoring:

A program was designed for the results of ambient monitoring, particularly as regards the handling of carcinogens. This was done in accordance with the conditions - registration of persons involved, measurement strategy and storage of the measured data obtained - laid down by the Employment Accident Insurance Fund, EAIF. The program for biological monitoring is in preparation. All these results can be collated with the occupational medical findings.

Occupational Medical Data

Personal data
Workplace history
Product exposure
Occ. med. examination
  (EAIF-principles)
Diagnoses (ICD)
Causes of death, tumors
Clinical laboratory
Shift, x-ray, ECT, spirometry
Audiometry
Accidents, intoxications
Billing

Methods

In the medical sector the following recallable, continuously updated and evaluable data are documented:

1. Selected personal data accessed on-line, from the personnel data bank, updated monthly, with about 65,000 records, including those of pensioners. Using a search program, these data are displayed on the screen, and include the plant where each person works and his job title.

2. A complete workplace case history has been documented, and is being kept updated, for each employee. This enables all personnel, including pensioners and those who have died, to be identified by means of a search program.

3. An internal four-digit code for working materials is used to record previous and current handling by personnel of specific materials, where this is not self-evident from the plant at which the employee works. It is applied also for chemical accidents.

4. The carrying out of occupational medical check-ups in Germany depends on the function or exposure to materials of the employee concerned. This is in line with so-called "principles for occupational medical examinations", recommended by EAIF. These recommendations for the examining physician comprise the specific questions to be asked, the course of the examination, and necessary and recommended supplementary technical investigations, and evaluation of the results. Regarded in Germany as the standard work for physicians practising occupational medicine, they currently contain 40 items which are constantly updated in the light of new findings. The exposure is coded with the appropriate number of the principle for storage.

   The code has been internally extended to cover other occupations or types of exposure outside the scope of this system.

5. All relevant diagnoses, whether obtained from the patient's case history or current, are encoded according to ICD (8th or 9th revision). These are added to the personal record on the tape.

6. The documentation on all causes of death, and all cases of tumours, comprehensive as far back as 1970 but previously restricted to deaths from cancer, is being extended by additional data on each employee's occupation, plant, workplace and exposure to materials.

7. Orders, working procedure and data storage for the clinical laboratory are at present merged off-line into the programme. Transfer of the results to the screen occurs in dialogue with a system plausibility check. The laboratory results are printed out on adhesive labels, to be filed on the medical record cards, and as a daily log. They are also allocated to the personal record in the memory. This provides the basis for an evaluation of laboratory parameters in respect of exposure to specific materials or of employment at specific plants.

8. Data regarding type of shift and the physician's aptitude assessments based on check-ups are stored in the dialogue. Medical treatment, supplementary investigations such as X-rays, ECG, spiroergometry, body box plethysmography, etc., are recorded, the results being encoded where possible.

9. Audiometric findings are stored by means of a numeric code, which indicates the degree of deafness in dB at the various frequencies.

10. Accidents and cases of poisoning are recorded separately by plant, time, type of injury, area of body and materials involved, the latter by the mentioned four digit code.

11. A monthly billing of all services provided is carried out, referenced by personnel numbers.

For these specific requirements, a program was designed for the IBM 8100 system (BCPMM). At present, the information system consists of 46 programs written in the programming language COBOL. Particular attention has been paid to data protection, bearing in mind the physician's duty of professional secrecy. In accordance with the basic rule of occupational medicine no medical data are given to the employer. This was the critical factor in the decision to install a decentralised computer in our own premises instead of using the mainframe computer at the computer centre. Right of personal access by our own medical personnel is restricted by a password, which is changed from time to time. The current data base is copied on magnetic tape for back up purposes and kept locked. The data filed in the central computer can be activated only from the Medical Department and are transcribed annually onto a tape and kept locked up in the Medical Department. Screens and printers have been installed for the daily routine of recording data for each individual patient in the technical office, the laboratory and the central input station. The patient is recorded by his personnel number, or via a search program using his name and date of birth. The personal data on the screen are checked for accuracy and then stored under a case number in an appointment data base within the system. This base can hold up to 3,000 records. The adhesive address labels necessary for routine procedures, with printed personal data, are used for forms, record cards, appointments, prescriptions, referrals, etc. After the conclusion of the examination, the medical data, diagnoses, materials code and other data are supplemented in dialogue.

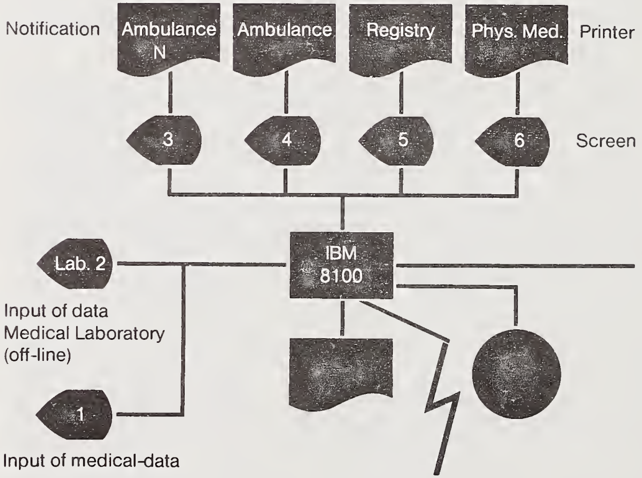

Figure 1

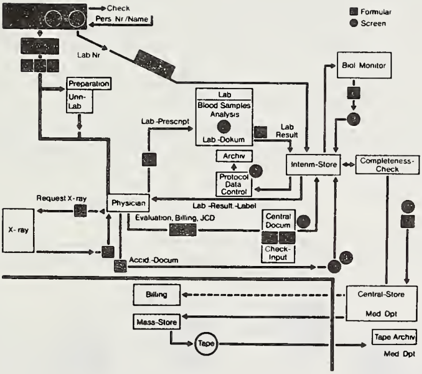

Figure 2

This medical part of the program has now been integrated with the results of the occupational hygiene surveillance. A quantitative assessment of risk requires a personalised record of measured data from the ambient and biological monitoring, stating as precisely as possible the nature, level and duration of exposure. Regulations have been drawn up in Germany in recent years referring not only to minimization of exposure but to an exact measuring program for monitoring it. The regulation applicable to carcinogens requires the specification of so-called work areas where the concentration of the materials is to be measured. The reference parameter is the TRC value (technical reference concentration), and the period of evaluation is one year. This threshold value for certain carcinogens, a special list of which is provided, is analytically monitored by a special measurement strategy. A similar strategy is used for materials for which a MAK value comparable to TLV exists. In this case, the time reference parameter is the working shift.

The system devised by us for this ambient monitoring contains three registers, namely:

A. Materials register with CAS number, TRC value, measurement procedure and recorded levels of concentration.

B. Plant register with numbered work areas, values for each shift and monthly means, and results.

C. Personnel register with personnel number and documentation on the beginning and end of each person's employment in the work area.

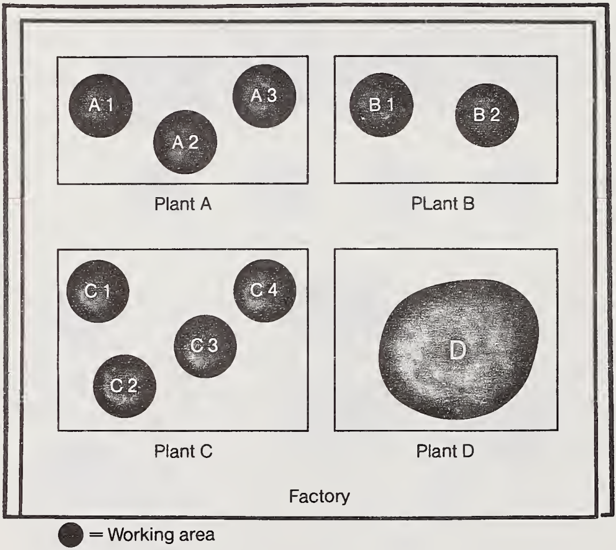

Figure 3

8. Studies of morbidity, as well as of mortality related to occupation, can be based on the records of all diagnoses for each case, especially those elaborated in connection with occupational medical examinations. These data are also useful for more extensive analyses for the purpose of epidemiological studies. A pilot program has been started for calculating expectation figures within the company. The availability of comprehensive records of causes of death for a comparison group of about 65,000 employees and pensioners makes it likely that the "healthy-worker" effect can be minimised.

The next illustration (figure 5) again shows the three modules of integrated data storage:

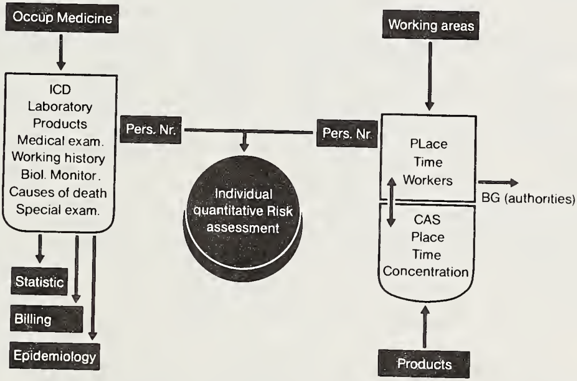

Figure 5

Medical data, such as diagnoses, laboratory findings, product exposure, findings from medical examinations, work history, biological monitoring, causes of death and findings from specific investigations provide the basis for a statistical and/or epidemiological reappraisal. The individual findings are allocated to the personnel number.

Products are defined by the CAS number. They are allocated to the work area; the period of exposure and the concentration level are determined with reference to work areas. These provide the basis for recording the employees working in them, who again are identified by their personnel numbers. The results obtained from collation of the three modules are used to produce an individual, quantifiable risk assessment. In many respects, this fulfils the conditions of a prospective epidemiological study.

Discussion

Comparison with other systems developed for the same purpose illustrates the remarkable variability of the systems, depending on production emphasis within the various sectors of industry. This is the reason why most companies have developed their own programs. In our program, we have given medical data equal priority with air and biological-monitoring findings. For principle reasons, we have in the medical sector given precedence to the encoding of medical diagnoses as opposed to the compilation of separate symptoms. Diagnoses and other assessments are based on the findings of experienced physicians. The computer can, and is intended to, make the physician's work easier and more effective without making decisions for him. Our system can be developed to allow for the storage of other parameters, such as testing of respiratory function, appointments scheduling and so on. In planning our ambient monitoring program, we had to allow for the current German regulations, laid down by government and by the EAIF, on established measurement strategies. These strategies enable us to state clearly whether or not a TRC or MAK value is being observed, or whether, in the sense of a predetermined definition, a working material has had an effect at all. To answer this question, the large number of perticular data elaborated by measurement can be calculated only by the computer.

Monitoring, based on measurement technology and classified by work areas, enables us to store all measured results over a long period, using a properly designed storage capacity. It is against this background that differences between our measurement and storage programs and those used in other countries should be seen. A major factor in these differences is the varying range of products and production processes.

Designing our program has taken our occupational medicine centre about seven years, until the commissioning of their own computer in April 1981. Today, start-up problems have been overcome, and validation procedures have ensured that the results are of excellent quality. Experience so far suggests that the same will be true for ambient and biological monitoring.

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APPLICATION OF A COMPUTERIZED OCCUPATIONAL HEALTH AND ENVIRONMENTAL SURVEILLANCE SYSTEM (COHESS) TO EMPLOYEES IN CHEMICAL PRODUCTION

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Abstract

In 1979, after three years in development, Diamond Shamrock Corporation completed a computerized occupational health and environmental surveillance system. With the assistance of this system, to date, 39 epidemiologic reports have been generated, many pertaining to employees engaged in the production of chemicals. Abstracts of four reports are presented and include:

1. Results of two consecutive dermatological surveys.
2. Comparison of baseline red blood cell cholinesterase and plasma cholinesterase values for male and female employees.
3. Review of serum hexachlorobenzene (HCB) values, and estimation of serum HCB half-life.
4. Review of the results of employee periodic health screening.

Résumé

En 1979, après trois années de travail, la Diamond Shamrock a terminé l'élaboration d'un système informatisé de contrôle de la santé professionelle et de l'environnement. Jusqu'à présent, le système a facilité la production de 39 rapports épidémiologiques dont plusieurs traitent d'employés qui fabriquent des produits chimiques. Les résumés de quatre rapports sont présentés. Ils comprennent:

1. Les résultats de deux études dermatologiques consécutives.
2. La comparaison de la cholinestérase de érythrocytes de base. Ainsi que des valeurs de la cholinestérase plasmatique des hommes et des femmes employés.
3. Un examen des valeurs de l'hexachlorobenzène (HCB) sérique, et une estimation de la demi-vie du HCB sérique.
4. Une étude des résultats de l'examen médical périodique des employés.

Introduction

In 1979, after three years in development, Diamond Shamrock Corporation completed a computerized occupational health and environmental surveillance system (COHESS). To date, 44 epidemiological reports have been generated utilizing the system, many of which pertain to employees engaged in the production of chemicals. Some of the findings are presented in this report.

Corporate medical and industrial hygiene program

The corporate medical and industrial hygiene program is the basis for our epidemiologic surveillance. Components of the program which contribute health related data to COHESS are as follows (Table 1):

1. Placement medical examination - Our medical staff has recognized the importance of reviewing all pre-employment or placement examinations prior to the employee's commencement of work in order to prevent improper placement with possible deleterious health consequences. The tests performed are similar to those offered in the periodic health screening examination. The findings provide baseline comparisons for both individuals and groups.

2. Periodic health screening - These examinations are conducted annually at most plants. They are available without charge to all employees on a voluntary basis and are performed at the plant site, utilizing a specially equipped mobile van, staffed by trained personnel, including a physician. The examination includes the following:

> Self-administered history, spirometry, chest x-ray, audiometry, visual acuity, ocular tonometry, electrocardiogram, blood chemistry (SMA-24), complete blood count with differential and red blood cell indices, urinalysis, blood pressure and pulse determinations, height and weight, and examination by a physician.

The follow-up to the periodic health screening examination includes the presentation to the employee of a computerized print-out of the findings and personal counselling by members of the health staff regarding any necessary additional examination or referral.

3. Special personal monitoring - Employees with a potential for exposure to certain chemicals are monitored on a routine basis with appropriate tests. For example, employees working with organic phosphate insecticides are tested weekly for blood cholinesterase activity. When activity levels are depressed, the employee is removed from exposure until the concentration has returned to within an acceptable range. In addition, an

analysis of the exposure and the use of required protective clothing or equipment is made and the employee counselled, if necessary. Employees are informed of the results of their personal monitoring.

4. Industrial hygiene and safety programs - These programs are highly integrated with the medical program for plant personnel. Investigations are frequently conducted on a team basis, utilizing members of the medical, industrial hygiene and safety staffs. The industrial hygienists conduct surveys of plants to delineate exposure zones and identify the materials and agents contained therein. Survey results and workplace monitoring data are incorporated into the computerized data bank.

TABLE 1: Diamond Shamrock Corporation - Corporate Health and Environmental Program

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1. Placement Medical Examination
2. Periodic Health Screening
3. Special Personal Monitoring
4. Industrial Hygiene Surveys and Monitoring
5. Occupational Accident and Illness Reports

Computerized occupational health and environmental surveillance system

Diamond Shamrock's computerized occupational health and environmental surveillance system provides the means for storage and analysis of vast amounts of health related data. Because of the speed by which data can be processed, epidemiological studies can be developed rapidly and relatively inexpensively. Great stress is exercised to insure that information incorporated into the system is valid and reliable.

The computerized program is divided into three modules (Figure 1). These relate to employees, plant locations and materials and agents, or more simply, PEOPLE, PLACES AND THINGS.

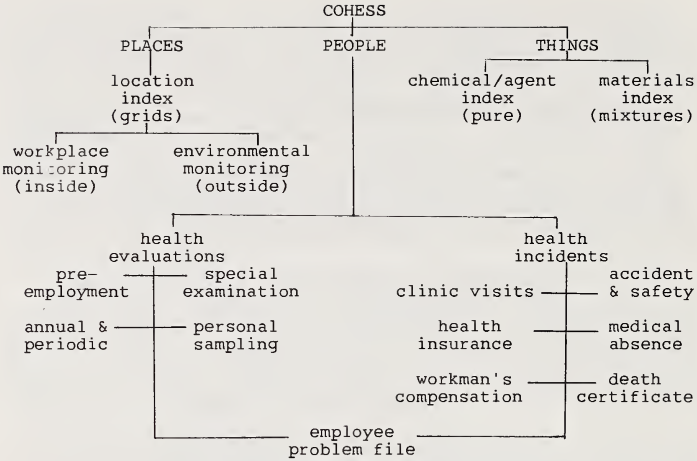

Figure 1: Organizational Outline

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1. Places module - Each facility is subdivided into broad geographical areas. Each area is further divided into zones which are coded. Zones are not equal in size nor similarly shaped, but similarity of exposure and activities throughout each zone is of prime importance. Materials and physical agents are identified by zone. Employees are identified also by zone and an estimate made of the percentage of time spent in each zone. (Epidemiologic considerations are necessary in comparing groups of employees on the basis of workplace location because an employee may work in more than one zone in a given period.)

2. People module - The People Module accommodates all employee health information. Stored in the system are data derived from pre-employment or placement examinations, periodic examinations, special examinations and personal sampling. COHESS can accommodate every item of health information, be it a history question, symptom, diagnosis, laboratory test or physiologic function test.

3. Things module - Within the Things Module, materials and agents present in company facilities are coded and stored. Chemical Abstract Service Numbers are used as a primary source of identification, when available. Physical agents such as noise and radiation are also entered.

Abstracts of epidemiologic reports

1. Dermatologic survey of a plant producing pesticides for agricultural use In 1978, the first of two skin surveys was conducted at the plant to assess the distribution of skin rashes among employees. One year later, a second survey served as a means of evaluating the effectiveness of the engineering and industrial hygiene controls that were instituted soon after the first survey.

The findings from the two surveys are compared (Table 2). There is a highly significant reduction in the percentage of employees with abnormal skin findings; 45.9% abnormal in 1978 versus 20.3% in 1979. Particularly important is the reduction from 21 cases of acute contact dermatitis in 1978 to none identified in 1979. Mild skin changes, suggestive of exposure to one of the products, a fungicide, were still evident in 1979, but at a much reduced rate.

2. Review of baseline red blood cell and plasma cholinesterase values, research center employees, 1980-1981 Baseline red blood cell and plasma cholinesterase values for employees at a research center were reviewed for the period July, 1980 - April, 1981. The values are the average of three determinations on blood specimens obtained at weekly intervals. Each specimen was taken on a Monday following a weekend without exposure to any known cholinesterase inhibitors. The test method used is based on the work of Ellman and the results are reported in International Units per liter. Twenty-two females and 80 males were tested. Of the 102 employees, 73 were assigned to laboratories and locations where carbamates are used. The remaining 29 employees had no work exposure to carbamates or other cholinesterase inhibitors.

For red blood cell cholinesterase values, there is a slight shift in distribution to lower values for females compared to males. This difference is not statistically significant (Table 3).

For plasma cholinesterase values, the shift to lower values for females is highly statistically significant ($p < 0.005$) (Table 4).

The observed difference in distribution of baseline cholinesterase values between carbamate and non-carbamate employees is not significant although there is a slight trend to higher values for the non-carbamate workers.

TABLE 2: Dermatological Surveys, Agricultural Pesticide Plant, 1978-1979

Physician's findings	1978	1979
Total Employees	157 (100.0)*	148 (100.0)
Normal skin	85 (54.1)	118 (79.7)
Abnormal skin**	72 (45.9)	30 (20.3)
dry skin	50 (31.8)	20 (13.5)
thinning of skin	14 (8.9)	11 (7.4)
yellowing of hands or feet	13 (8.2)	3 (2.0)
scaling or flaking	10 (6.4)	3 (2.0)
macules & papules	9 (5.7)	4 (2.7)
erythema, generalized	7 (4.5)	1 (0.7)
pruritus	7 (4.5)	0 (0.0)
unclassified	3 (1.9)	5 (3.4)
acute contact dermatitis	21 (13.4)	0 (0.0)

* Percentage of employees with a given finding is shown in parenthesis

** Some employees had more than one abnormal finding

TABLE 3: Distribution of Baseline Red Blood Cell Cholinesterase Activity Values, by Sex, July 1980 - April 1981

	RBC CHOLINESTERASE ACTIVITY VALUES (IU/L)			
Sex	4000	4000-5000	5000	totals
Female	5 (22.7)*	15 (68.2)	2 (9.1)	22 (100.0)
Male	8 (10.0)	63 (78.8)	9 (11.3)	80 (100.0)
Totals	13 (12.7)	78 (76.5)	11 (10.8)	102 (100.0)

* The percentage of the total for each sex is shown in parenthesis

TABLE 4: Distribution of Baseline Plasma Cell Cholinesterase Activity Values, by Sex, July 1980 - April 1981

	PLASMA CHOLINESTERASE ACTIVITY VALUES (IU/L)			
Sex	4000	4000-5000	5000	totals
Female	12 (54.5)*	8 (36.4)	2 (9.1)	22 (100.0)
Male	10 (12.5)	51 (63.8)	19 (23.8)	80 (100.0)
Totals	22 (21.6)	59 (57.8)	21 (20.6)	102 (100.0)

* The percentage of the total for each sex is shown in parenthesis

3. Review of plasma hexachlorobenzene values, employees of a plant producing pesticides for agricultural use Plasma hexachlorobenzene (HCB) values, monitored in conjunction with the periodic health screening program, were reviewed for a plant producing pesticides for agricultural use, for the period 1978-1981. Employees in the unit producing a pre-emergent herbicide showed generally higher values than those at other locations in the plant. (Table 5). Airborne HCB concentrations were also highest in the herbicide unit (Table 6). A shift to higher plasma HCB values among employees with earlier hire dates was also demonstrated and remained statistically significant even when adjustments for age were made. Plasma HCB half-life was estimated at 1.17 years. Engineering changes to reduce the levels of exposure have been instituted.

4. Review of employee annual health screening reports, research center, 1980-1982 As part of the health surveillance program, the results of the annual health screening of employees at a research center were reviewed. The distributions of values for 28 selected test parameters were compared with expected distributions. In addition, the distributions among years for the period 1980-1982 were examined for evidence of significant changes or trends (Table 7). Employees with test values highly suggestive of a problem (usually one standard deviation or more beyond the reference range) had their health records reviewed in greater detail.

TABLE 5: Annual Employee Health Screening. Distribution of Cumulative Serum Hexachlorobenzene (HCB) Values, by Selected Work Locations, * 1978-1981

Work Location	SERUM HCB VALUES (ng/ml) 100	 100-400	 400	Totals
Herbicide unit	13 (12.7)**	68 (66.7)	21 (20.6)	102 (100.0)
Fungicide unit	60 (44.8)	68 (50.7)	6 (4.5)	134 (100.0)
Quality control laboratory	35 (71.4)	13 (26.5)	1 (2.0)	49 (100.0)
Offices	72 (85.7)	11 (13.1)	1 (1.2)	84 (100.0)
All other locations	157 (45.4)	155 (44.8)	34 (9.8)	346 (100.0)

* Included are employees who spend a minimum of 50% of the work day in the location

** The percentage of the total for each sex is shown in parenthesis

TABLE 6: Personnel Monitoring. Airborne Hexachlorobenzene Concentration (micrograms/cubic meter), by Percentile and by Selected Work Locations, July 1978-December 1980

Work Location	Number of Samples	CONCENTRATION BY PERCENTILE 50th	 90th	 100th
Herbicide unit				
process	120	5.3	47.9	5560
formulation	8	3.0	18.6	29
packaging	12	0.0	5.3	17.7
maintenance	134	2.3	16.6	243
Fungicide Unit				
process	102	0.4	2.5	20.6
maintenance	168	0.4	5.1	818
formulation	34	0.1	2.2	24.2
Quality Control laboratory	67	0.5	2.1	33.2
Offices	10	0.1	0.9	2.2

TABLE 7: Annual Employee Health Screening. Distribution of Values for Selected Serum Tests, 1980-1982

	Number of Employees Tested (Percent of Values Within Reference Range)		
Test (Reference Range)	1980	1981	1982
Urea Nitrogen (7.0 - 23.0 mg/100 ml)	370 (98.1)	404 (96.5)	287 (97.6)
Creatinine (0.4 - 1.5 mg/100 ml)	369 (98.9)	404 (99.8	285 (99.3)
Glucose, non-fasting (65 - 160 mg/100 ml)	369 (96.5)	404 (96.0)	285 (98.2)
Uric Acid (2.5 - 8.0 mg/100 ml)	369 (95.7)	404 (95.0)	285 (93.7)
Cholesterol (250 mg/100 ml)	369 (88.6)	404 (85.4)	285 (90.2)
Triglycerides, non-fasting (200 mg/100 ml)	369 (80.0)	404 (84.4)	285 (89.8)
Total Protein (6.0 - 8.0 g/100 ml)	369 (97.8)	404 (99.3)	285 (98.9)
Albumin (3.5 - 5.0 g/100 ml)	369 (100.0)	404 (100.0)	285 (100.0)
Globulin (2.0 - 3.5 g/100 ml)	369 (98.9)	404 (98.5)	285 (96.8)
Total Bilirubin (0.2 - 1.2 mg/100 ml)	369 (94.6)	404 (94.3)	285 (94.0)
SGOT (0 - 40 IU)	369 (98.1)	404 (99.3)	285 (97.9)
SGPT (0 - 40 IU)	369 (93.5)	404 (91.3)	285 (93.0)
GGTP (0 - 62 IU)	369 (96.5)	404 (97.8)	285 (97.5)
Alkaline Phosphatase (30 - 115 IU)	369 (96.2)	402 (97.0)	285 (96.5)

Overall, the distributions of health measurements remained fairly stable in the period under review and no unusual clustering of disease or disordered physiology was identified.

Conclusion

A dynamic occupational health and environmental surveillance system has been described. Essential to the system is the gathering of useful, valid and reliable data. The surveillance processs has been markedly enhanced by the availability of a computerized data system which we call COHESS. In turn, the findings have been translated into improvements in work conditions and the promotion of good health practices for our employees.

"HYDRO HEALTH" THE NORSK HYDRO SYSTEM FOR PROCESSING ADMINISTRATIVE-EPIDEMIOLOGICAL DATA

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Abstract

Health and occupational measures are collected together in an occupational health database. The base is created for scientific epidemiologic studies, and, at the same time, for daily health care purposes. For each person the following pictures are presented at a screen and linked together.

1. Personnel system,
2. work and exposure history,
3. work history outside the actual factory (preoccupation),
4. system for selective health control,
5. laboratory system,
6. system for social history,
7. education,
8. injuries,
9. history,
10. history of self exposure,
11. medicaments,
12. rehabilitation,
13. sickness in family,
14. journal,
15. x-rays,
16. absences from work.

Three years of work and 10 million Norwegian crowns were used to create this system.

Résumé

Mesures dans les secteurs de la santé et du milieu de travail, intégrées à une base de données sur la santé professionnelle. La base a été créée pour les études épidémiologiques scientifiques ainsi que pour l'administration quotidienne de soins médicaux. Pour chaque personne, les données suivantes sont présentées sur un écran et intégrées:

1. système personnel,
2. antécédents de travail et d'exposition,
3. antécédents de travail à l'extérieur de l'usine (préoccupation),

4. système de contrôle sélectif de la santé,
5. système de laboratoire,
6. système pour les antécédents sociaux,
7. formation,
8. blessures,
9. maladies,
10. antécédents d'auto -- exemeus,
11. médicaments,
12. réhabilitation,
13. maladies dans la famille,
14. journal,
15. rayons-X,
16. absentéisme.

Projet créé au prix de trois années de travail et de 10 millions de couronnes norvégiennes.

Introduction

Norsk Hydro, an industrial company with headquarters in Oslo, Norway, has approximately 20,000 employees, and is engaged in the whole range of activities connected with oil and gas production - prospecting, exploration, drilling, refining and distribution. We are the world's twentieth largest oil company and we are considerable producers of hydro-electric power. We are one of the world's three largest fertilizer producers and we also produce industrial chemicals and gases, petrochemicals and the light metals aluminium and magnesium. Our sales world-wide are currently running at well over 3 1/2 billion dollars a year.

In the course of the years 1980-1983, the company's health department has developed a system for processing administrative-epidemiological data, which we have christened "Hydro-health".

The system

Generally speaking the system can be divided into three sections: a personnel and notification system, a laboratory system, and a system for the historical storage of medical data.

Hydro-health program

- personnel notification system
- laboratory system
- historical storage of medical data

The personnel and notification system contains the following functions:

- Personnel
    - staff register
    - notification
        - occupational data
        - listing of notifications
        - form
            - department directory
            - time schedule
            - documents

Once a month information on staff changes is transferred electronically from the company's personnel section to the health department computer. In addition all information about where the individual has worked before is stored historically. In this way it is possible to have accurate information about all staff currently employed, and we can establish in what jobs individuals have been employed previously.

Display: Staff Register

Soc. Sec. No.	____________	Name	____________
Final Code	____________	First Employed	____________
Job Title	____________	Type of Work	____________
Salary	____________	Hiring Code	____________
Sex	____________	Marital Status	____________
Address	____________	Phone home	____________
Township	____________	Phone work	____________
Employee No.	____________	Employment terminated	____________
From Date	____________		
Department -Section	____________		

Some of these inserts will vary with time, (department, salary, job title, etc.). This display will always show the latest (most relevant) values.

The laboratory system consists of the following functions. This is a highly flexible system. In the analysis register we can at any time, within a minute, define a new lab test. It is also possible to define and redefine the order in which the results are printed out for storage in the patient's Medical Record. The computer will also automatically call our attention to any laboratory results that exceed reference limits.

Laboratory
- summary analysis
  - results analysis
    - status analysis

Display: Analysis Register

Analysis ______________________
Unit ______________________
Output Category ______________________

Response Category ______________________

Lower Reference Limit Males ______________________
Lower Reference Limit Females ______________________
Lower Rejection Limit ______________________

Frequency of notification ______________________
General Status-Analyses ______________________

PROBLEM: There is a need to be able to define and store, quickly and flexibly all possible biological and environmental tests, applying to individuals, departments, work stations and jobs. It must be possible to redefine the parameters for the interpretation of such tests in step with current research results, and for the working environment in step with the latest administrative regulations.

For any one individual the analysis results are displayed as shown in the following display. An asterisk suggests that the result exceeds the reference limit whereas an exclamation mark shows that the result exceeds the rejection limit, whereas an exclamation mark shows that the result exceeds the rejection limit. The latter can lead to immediate action where exposure is concerned.

Display: Analysis Results (per individual)

Soc. Sec. No. ____________________ Name ______________________

Date	Analysis	Result Unit	Comment
120475	S-Ca Serum Calcium	16.0 nmol/pos	14 Hemolysis
030481	U-Hg Urine Mercury	515 nmol/l	1 Alternative Work
......	....	....	....

By having displayed analysis summaries for all individuals who are exposed to mercury, the work environmental factors in this particular field can be speedily monitored on a continual basis. This, of course, goes for all other person related laboratory tests as well.

Display: Summary Analysis (several individuals)

Soc.Sec.No.	Date	Analysis Result	Unit	Comment
631 419 328	121279	U Hg	629 mmol/l	1 Alternative Work
639 220 385	010180	U Hg	550 nmol/l	1 Alternative Work
....	......	....	....	....

PROBLEM: There is no need to be able to obtain a quick assessment of how biological and job-environmental tests have turned out for individuals, departments, work stations and jobs.

In the main, work environmental data are stored in three displays. In the display combining department and exposure environmental information is stored about places of work in various well defined geographical locations.

Environmental Data
- department-exposure
  - job-exposure
    - diagnosis-exposure

Display: Combination Department-Exposure

Exposure	Department/ work station	From MMYY	To MMYY	view	M/E	Exp	A	Persons at risk
1 Asbestos	Foundry	0105	1179	MU	–	–	A	50
1 Asbestos	Foundry	1279	0280	MU	M	S	B	85
....	....	....	....	..	.	.	.	..

PROBLEM: The health department has to know where and in what amounts various environmental agents occur. Increase or decrease in environmental problems must be recorded.

In this way all places of work in the company can be plotted. We can then see how various environmental agents affect the work environment in different parts of the company, and how these vary with time. When the personnel system contains information on who has worked where it is possible to do epidemiological research easily and economically.

For individuals who do not have a fixed place of work, but move from place to place, the situation is more complicated. As a basis we take a particular job and measure the exposure related to it. We then say that anyone else with this same job has the same degree of exposure. This is something we are not keen on doing since it is a time consuming task to keep a record of all individuals who have a special job. But, when necessary, we do in fact update our information on all those with special jobs.

Display: Combination Job-Exposure

Exposure	Job	From MMYY	To MMYY	1.view	M/E	Exp	A	Persons at risk
23	cinder worker	1170	1281	UT	M	S	B	135
23	cinder worker	0182	0384	TF	M	N	C	135
....	....	....	....	..	.	.	.	...

PROBLEM: The health department must have knowledge of what kinds of exposure the various jobs are connected with.

Display: Employee Job-History (at Hydro)

Soc. Sec. No. __________ Name: ______________________

From	To		Comments/type of job/exposure time
0375	0376	Hard plastic	Manual contact with epoxy 20% of working hours
0476	0378	Hard plastic	Spraying of epoxy 40% of working hours
....	....	....	....

PROBLEM: The health department should recognize persons employed in jobs with a high environmental risk-load, it is necessary to recognize the relationship between exposure and effects on health.

Certain individuals have diseases that can be aggravated by exposure to a certain kind of unfavourable environment. To avoid persons at risk ending up in such environments by accident, we have the ability to run a program to check this. For example if a patient with known glomerulonephritis is put to work in an area with a high risk potential for mercury, the computer will warn the health department. The department will then look into the individual case.

Display: Combination Diagnosis-Exposure

Environmental Agent	Detrimental to Diagnosis
12 Asbestos	15600 Asthma
229 Mercury	58000 Glomerulonephritis
35 Lead	27900 Porphyrinuria
....	....

PROBLEM: There are individuals who have, or can contract diseases that can be aggravated by certain work-environmental factors. The health department will need a system to prevent this from happening.

The third main constituent of the Hydro-health program is the historical storage of medical data. Here I only intend to show examples taken from the most important aspects of this part of the program.

Medical Data

Health Check
Injury Registration
Injury History
Medical Record
Self Imposed Hazards
Documents
History of Illness
Summary of Illness

Rehabilitation
Present Occupational History
Familial Illness
Previous Occupation History
Diagnosis When Absent
Education
External Occupational History
Medicament Comsumption

Display: History of Illness

Soc. Sec. No. ________ Name: ____________

Year	Diagnosis	Diagnosis-text	Reported SAT/RTV	Doctor
1968	41200	Agina pectoris	...	OLSEO
1970	72500	Sciatia dxt. prolaps L4	...	TSS
....	.....	....	...	....

PROBLEM: To run a health and environmental service, it is necessary to list all the most important illnesses each individual has had or is still suffering from.

Illnesses brought to the knowledge of the health department through health check ups or in other ways, are stored as shown below. The illnesses are classified according to the "international classification of health problems in primary care". This display makes daily contact with the patient easier, is part of the basis for selective health checks and is important in connection with the work environment and problems of where to place employees.

Display: Illness Listing

Diagnosis	Year	Soc. Sec. No.	Diagnosis-text	SAT/RTV	Doctor
25000	1980	170218 29543	Diabetes	...	OLSEO
25000	1982	111162 12587	Diabetes	...	TSS
....	.....	....	....	...	......

PROBLEM: To run a health and environmental service, it is necessary to list all the most important illnesses each individual has had or is still suffering from.

The medicament and drug consumption of individual staff members has been systematized according to the Scandinavian medical chemical pharmaceutical index. At the present time we know very little about what hazards chemical exposure to medicaments and drugs represent, especially seen in connection with work environment exposure. This could possibly become a basis for further studies.

Display: Consumption of Medicaments

Soc. Sec. No. __________ Name: ____________________________

Date	Medicament	Date of Reiteration	Strength/unit /dose/no.	Note
1280	A12B 1VA01 Valium	040483	5 mg 1 tab. p.n.	
1280	C07A A0905 Tenormin	100880	50 mg 1x2, 200A1	12 g
....	....	......	....	.....

PROBLEM: In normal medical practice, a record of any patient's medication at any time is essential. When dealing with work-accidents and epidemiology the same is true.

In all epidemiological investigations it is essential to know what external hazards people expose themselves to. In the display, "Self-imposed hazards", it is possible to store such information. To us it is primarily a question of knowing about individual smoking habits, and such information is available on all employees. Furthermore the possibilities for storing information on self-imposed exposure are legion and here we can for example store information about membership in the company sports team. It would doubtless be interesting to look more closely into the relationship between accidents and absence among these individuals.

Display: Self-Imposed Hazards

Soc. Sec. No. __________ Name: ____________________________

From Date	To Date	Hazard Factor/ Material	Dose per day
010147	311275	1 Tobacco	7 g
011080		1 Tobacco	14 g
......	......	....	....

PROBLEM: It is essential to know what hazards people expose themselves to in order to conduct preventive medicine, selective health checks, epidemiological research etc.

An important function of the health department is to monitor the individual's absence from work, and assist where needed. Once every month, information about absence is transferred from the company's wages department to the health department. Sickness reports from the local social security office are added to the information on each individual case of absence and stored for each patient. This information is made available to the doctor as shown on the display.

```
     Display:  Absence-Diagnosis of Employee

Soc. Sec. No.  __________      Name:  ____________________________

From    To      Diagnostic Code          Type  Text         Doctor

030782  949682  99999 Doctor not seen     D    Abdomin      OLSEO
121082  251082  71420 Asthma              A    Asthma       KORSK
......  ......  .....................     .    ..........   .......
```

PROBLEM: For the health department an important function is to monitor the individual's absence and assist where needed.

Seeing that accidents from time to time are connected with medical factors, such as diseases, drugs etc., all work accidents are listed and analysed by the health department.

```
     Display:  Injuries

Soc. Sec. No.  __________      Name:  ____________________________

Date: 270783    Time: 0940     Place: 50900 Mg. foundry furnace 2
Ordinary hours/shift (O/S): 2
Part of body: 3  Trunk     Accident:      126 Spray from Smelt
Injury:       7  Burn      Job Category:   11 Furnace Operative
Activity:   501  Casting   Equipment:       4 Foundry Furnace
Absence:     40
Other personnel involved (Y/N): N
Technical/Material Insufficiency (Y/N): Y

Comments:  Damage on heat-resistant material in casting trough
```

PROBLEM: There is a need to register work-accidents in order to be able to prevent new ones, to meet legal requirements and to find out whether accidents may have any connection with medical factors.

Naturally, the system contains a medical record, and here a word processing system allows us to write freely. The word processor has all the normal editing functions and thus makes it possible to produce a more readable text than is to be found in an ordinary medical record.

Display: Medical Record

Soc. Sec. No. ___________ Name: ___________

Name of Document	Type	Enter Work Proc. Syst. and se/alter Document X	Number of Signs
Medical Record	....	X	1365
Records	....	X	....
....	....	X	....

PROBLEM: Some problems cannot be categorized, and space for recording these is necessary.

Display: Medical Record

Soc. Sec. No. ___________ Name: ___________

020182 During the last few days, pain in left thorax radiating to left arm. ECG gives suspicion of infaction, admitted to hospital

250482 Pain left maxillary sinus, cold symptoms with cough. Sinusitis. Penicillin Tab. 0.32 g 1x3x10

060582 Angina pectoris, Tenormin tab. 50 mg x2

PROBLEM: Certain problems cannot be categorized, and so a free recording of these is needed.

Because of the time factor, I do not intend to go into details on external occupational history, education, familial diseases, rehabilitation, social registration, the possibilities for storing documents in plain text, nor the setting up of some 30 different registers.

I have so far only talked about the possibilities that exist for storing health and environmental data. However, the really interesting facts come from pulling out data and comparing one set with another through a general report generator. In this way we can combine health and environmental data in any way we wish. For example accidents and their connection with central stimulating drugs, noise with reduced hearing etc.

Display: External Occupational History

Soc. Sec. No. ____________ Name: ________________________________

From Date	To Date	Occupation Classification	Company	Exp. Fact.	Unit	Degree 0-9
070770	010672	61220 Deck hand	Kosmos	Noise	dB	8
020672	311274	61210 Seaman	Kosmos	Noise	dB	8
.....	......	....	......	.....	..	.

PROBLEM: In occupational medicine it is very important to know what kind of unfavourable job-environment the individual has been exposed to, including the time prior to his engagement with Norske Hydro.

Display: Education

Soc. Sec. No. ____________ Name: ________________________________

From	To	School, Course, Duration	Result
1976	1979	High School	Passed
1979	1981	College, Economy	Passed w. honors
....	....	....	....

PROBLEM: To do research it is desirable to be able to classify the staff in social groups according to education.

Display: Familial Disease History

Soc. Sec. No. ___________ Name: ________________________________

Relative	Born Year	Diag. No.	Diagn.- Text	Onset Age	Death Diagn.	Diagn. Text	Death Age
WI	25	2500	Diabetes	12	41000	Myoc. inf.	65
BR	13	2500	Diabetes	15	41000	emboly	73
..	...	....	....	..	.....	....	..

PROBLEM: Hereditary diseases can be important knowledge in selective health checks. In evaluating the need for social support it is useful to recognize the disease-load in the family circle.

Display: Rehabilitation

Soc. Sec. No. ___________ Name: ________________________________

From Date	To Date	Reason	Reaction/treatment
020182	050382	9 Alimentary Disease	1 Rehab. Workshop
060382	000000		7 Other work in dept.
......	......	....	....

PROBLEM: The company has its own rehabilitation workshop and conducts active rehabilitation of employees. A summary of this work is desirable, in order to evaluate and improve this activity.

```
     Display:  Social Register

Soc. Sec. No. __________     Name: ____________________________

Reason for Reg.                    ____________________________

Date of Reg.                       ____________________________

Reporting Freq.                    ____________________________

Contract Signed Date               ____________________________

Contact Person No. _______   Name: ____________________________

Date    Type    Text
           A  Drunk when reporting for work.
           S  Domestic problem, home help provided, working again
           S  All well, has received help to repay his debts
           A  Drinking again.  Admitted alcohol clinic
           S  Working again, Disulfiram
```

PROBLEM: In order to be able to render service and to monitor the progress of those who receive help from the AKAN treatment (AKAN- National committee against alcoholism and drug abuse), the national department needs to have this work recorded.

```
     Display:  Documents

Name:  ____________________________

020182   History          Tbc. skintest pos. acc. to pat. BCG
                          54. 1983 Pulmonary Tbc. 1977 Pulmonary
                          asbestosis.  1980  Myoc.  inf.  High
                          degree of asbestos exposure.

010582   x-ray cor/pulm   Left ventricle enlarged

030282   x-ray chest      Mediastinal  tumor.  Pleurisy  in
                          lateral posterior field.  Fibrosis
```

PROBLEM: Some problems cannot be categorized, and space for recording these freely is necessary.

An absence report program produces a listing of non-appearances grouped according to age, sex, place of work, 600 different job titles, 5 kinds of shifts etc.

A hearing report program would monitor hearing capability of all employees and warns the health department when any deterioration takes place. It is possible to list all those who, since their last audiometric test have had a reduction of 20 dB or more in the 4,000-6,000 Hz. frequency range.

As you will realize, many further possibilities exist for report programs, but there would be little point in going into more detail at this time.

Norsk Hydro's health department has been gradually undergoing a change in character ever since the system, which I have described, was first started up.

We started off by being mere lookers-on where environmental questions were concerned. Recently we have started taking the initiative on such questions and are now leading the way when it comes to finding solutions.

Our aim, which is to get the individual on the shop floor to see the health department as a positive and material contributor when it comes to tackling environmental problems, now seems to have been attained.

A USER-DRIVEN OCCUPATIONAL HEALTH INFORMATION SYSTEM

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Abstract

The rapid advances in occupational health make it mandatory to correlate data from many sources in disciplines such as medicine, industrial hygiene, toxicology and safety. In order to utilize the information effectively requires that the health professional be able to interact directly with the data, have access to information on an ad hoc basis, and be able to use statistical analysis tools, all without having to acquire sophisticated programming skills.

Prior attempts to address the problem utilizing traditional data processing techniques have been costly to develop, difficult to modify, and have allowed only limited user interaction with the data.

This paper discusses the application of a generalized Data Base Management System (DBMS) to create an occupational health information system which is relatively inexpensive, easy to modify and provides direct user interaction without major application programs. Two corporations - one with a single large operation, the other a multi-national with widely dispersed operating units, are currently developing occupational health information systems using the same DBMS. Scientific Information Retrieval (SIR)/DBMS is a comprehensive DBMS which supports the hierarchical data base model and the ability to link multiple hierarchies into a network structure. Data can also be assessed using the relational data base model. This approach provides the tools to allow the retrieval and correlation of the complex and widely diverse information that is needed to operate effective occupational health programs.

A detailed discussion of the criteria for development of such a system will be presented. These criteria evolved over a 3-year period and were tested in a pilot study utilizing data from all of the sources and disciplines for a subset of the employee population.

Of particular importance has been the direct involvement of the user groups in the development process. This has resulted in an effective user driven system which has the ability and flexibility to be tailored to the specific requirements of virtually any occupational health setting.

Résumé

Les progrès rapides réalisés dans le secteur de la santé professionnelle ont rendu nécessaire la corrélation des données provenant de nombreuses sources à l'intérieur de disciplines telles que la médecine, l'hygiène industrielle, la toxicologie et la sécurité. Afin d'utiliser les données de façon efficace, les professionnels de la santé doivent pouvoir se servir de façon interactive directe de l'information, avoir accès aux données sur une base ad hoc, et employer des outils d'analyse statistique sans devoir acquérir des connaissances approfondies en programmation.

Les tentatives antérieures visant à solutionner le problème au moyen de techniques traditionnelles de traitement des données ont été des expériences coûteuses quant à la mise au point du système et à ses modifications postérieures, et n'on permis qu'une interaction limitée de l'utilisateur avec les données.

Le présent mémoire traite de l'application d'un système généralisé de gestion de base de données (S.G.B.D.) en vue de créer un système d'information sur la santé professionnelle qui soit relativement peu coûteux, facile à modifier et offre à l'utilisateur la possibilité d'interaction sans l'emploi de programmes majeurs d'application. Deux corporations, l'une étant une seule exploitation importante et l'autre, une entreprise multinationale comportant des unités d'exploitation très dispersées, mettent au point actuellement des systèmes d'information sur la santé professionnelle à l'aide du SGBD. Le Scientific Information Retrieval (Extraction des Données Scientifiques) (EDS)/SGBD constitue un SGBD global qui soutient le modèle d'une base de données hiérarchiques et la capacité de relier plusieurs hiérarchies dans une structure de réseau. Les données peuvent également être évaluées à l'aide du modèle d'une base de données de relation. Cette approche permet l'extraction et la corrélation des donnes complexes et très diverses nécessaires pour l'exploitation efficace de programmes de santé professionnelle. Un exposé détaillé des critères pour la mise au point d'un tel système sera présenté. Ces critères ont été élaborés au cours d'une période de trois ans et ont été mis à l'essai lors d'une étude pilote utilisant des données provenant

de toutes les sources et disciplines pertinentes à une série mathématique de la population des employés. La participation directe des groupes d'utilisateurs dans le processus d'élaboration a pris une importance particulière. Elle a permis la mise au point d'un système efficace commadé par l'utilisateur avec possibilité d'adaptation aux exigences particulières de presque n'importe quel contexte de santé professionnelle.

A user driven occupational health information system

This presentation will describe our concept of an occupational health information system, the facilities required to manage the database and to use it for daily informational purposes, as well as for epidemiological investigations. We feel that new approaches to handling occupational health information must be put to use before the monster takes over. By describing the combined experiences of two companies involved in a design and implementation process of an OHIS we hope to provide some insight into a recurring problem in occupational health: that is, making sensible, effective use of the large volumes of data available to the health professional. Throughout this description, the concept of a "user driven" occupational health information system will be defined.

The main points of this talk are based on concurrent development of an occupational health information system at two companies, namely, Dofasco, Inc. an integrated steel producer in Hamilton, Ontario, and INCO Ltd., the world's largest nickel producer, with head office in Toronto, Ontario. The development of the OHIS at these two sites has followed a highly similar path, even though the two companies have very different organizational structures. Whereas Dofasco is a highly centralized organization employing 12,000 employees, with one centrally active medical clinic, INCO has operating units throughout the world, some with their own central clinics, using a variety of computers and subject to many diverse national laws and regulations. Both companies have an epidemiologist on staff that carried out the majority of the development of this system in conjunction with a DBMS.

The presentation will consist of four main sections starting with our combined experiences defining the design criteria and proceeding through our design process and principles. I will finish with a brief discussion of the OHIS product that is being developed based on our experience.

Design criteria

It is quite common in industry, and also true at Dofasco and Inco to find that all computer systems are designed and maintained by the systems department with actual user input confined to the definition of a problem and a statement of the required input and output.

In our situation, however, it was felt that there were requirements for flexibility that could only be achieved in a system that was "user driven". By "user driven" I mean that the user group itself must be able to carry out many essential operations with minimum assistance from computer systems personnel.

Among these operations are:

1. Generating the initial database definition.

2. Altering the definition throughout the life cycle of the database by adding or subtracting variables or by changing the description of the variables, their values and value ranges etc.

3. Creating reports and retrievals whenever required.

4. Modifying the format and content of existing reports.

5. Conducting epidemiological studies in which one must be able to execute new retrievals, generate summary files and apply complex statistical analyses to the data.

To achieve such a situation is by no means an easy task. To build a system from the ground up with this flexibility and with all the useful properties of DBMS systems would surely require many programmer years of work.

It is evident that only a full fledged database management system would provide the necessary facilities to perform these operations and allow a user to perform them.

The users may be researchers or research assistants, doctors, nurses, clerical staff, administrative people or managers. We are talking about people who will obviously have to undergo a certain amount of training in the use of the system but whose primary function is not in computer systems or programming.

Most sites will want to have a database administrator whose primary function will be to ensure that operations affecting the database are carried out correctly and on time.

Design process

Let me briefly describe the design process we went through.

The first step in building a tailored system was the formation of a user group composed of representatives from all of the departments that would be contributing to and using the database system. This group included representatives from the Medical Department, Industrial Hygiene, Safety and Personnel.

Data to be included would be gathered from the Emergency Care Clinic, Periodic Health Exams, Safety and Accident Records, Material Safety Data Sheets, Industrial Hygiene Monitoring, and Workers' Compensation Records.

The group's first task was to carry out a literature search and to contact any large companies who might have an OH information system suited to our needs. Although there were quite a few systems in operation we found that none had the flexibility that was required and none were of a similar magnitude in terms of amount and variety of information we wanted to include. The obvious conclusion was that it would be necessary to build our own.

The user group met weekly for about six months. Every week jobs were assigned to members to assist in defining the format, availability and reliability of data in specific areas and gradually a detailed definition of the required data and the relationships between data items was built up entirely on paper. Record type structures were defined, containing all the required data variables complete with formats, coding systems and labels.

With the data defined, the problem of what specific tools to use still remained. Rather than spending the considerable resources required to build our own database management system, we decided to lease one of the many DBMSs currently available. That which seemed most flexible and suited to our requirements was SIR/DBMS and its complementary subsystems: SIR/FORMS and SIR/SQL+.

SIR (Scientific Information Retrieval) was designed specifically to meet the needs of scientific research, decision support and data analysis. To use SIR, one utilizes the interactive editor to define the security desired, the relationships between data types and a complete description of each type of record. Once the study schema is defined, data may be entered either interactively or by batch data entry.

SIR/FORMS is an integrated subsystem for interactive, screen-oriented data entry and retrieval.

SIR/SQL+ is an interactive relational query system that lets users interrogate and update their databases using simple English language commands.

Both of these abilities are definite requirements of a successful OHIS.

The system also provides a retrieval language and report writer with which procedures can be written for retrieving data from the database for generating reports or for creating rectangular system files for direct access by one of the major statistical packages such as SPSS, BMDP, or SAS. To fulfil the analytical requirements of the epidemiological studies, the integration of one of these packages into the information system is a requirement. The database system also provides standard options for unloading the database to tape for storage or moving to another computer.

Design principles

Given the preceding development process, the group identified the following principles which must be addressed when creating an OHIS.

Flexible usage

In occupational health, the nature of the data is such that different users will have different uses for the same data item. This emphasizes the need for user input in the design stage to ensure that most uses will be identified. The requirement on the system side is that it will often be necessary to access a particular record via different pathways.

Use of existing information

It makes little sense to throw away already existing data or programs if you have the ability to integrate old information into a new system. An important point here is that mechanisms must be in place for updating this information to maintain an accurate database. This is particularly important when a number of collection centres are being linked.

Documentation

As mentioned previously, to make efficient use of stored information, the users must know and easily understand the data available to them. This is accomplished by requiring user input during the development of the OH information system and by maintaining a well documented data dictionary or codebook description of the database preferably both online with the system and in separate hard copy.

Ease of use

The system must be designed in such a way that the users are able to sit down at a terminal and easily get at the information they want. This is done in our system by simply running an existing program written with the retrieval language and report generator or by using the relational query language. You should not have to request each job from the systems group.

Spontaneous request handling

Essentially this means that any reasonable request can be handled without undue programming intervention. For example, suppose you are tracking the distribution of a few thousand chemicals around your plant and have an industrial hygiene monitoring program. When the Journal of Occupational Medicine publishes a paper describing serious and previously unknown effects from exposure to a particular substance, you want to be able to identify who has been exposed and, at what exposure without having to wait a month for the programming crew.

Easy change

Of prime importance is that the database can undergo additions, deletions and changes without interfering with the organization of the data. Since occupational health record keeping is undergoing rapid change, it is difficult to assess what will become important in the future and what information will turn out to be useless. Additions and deletions of various types must be allowed by the DBMS without massive reprogramming.

Cost containment

The best method of minimizing cost is by effecting planning. This usually means development of the system on paper extensively before using the computer. The size of your database will greatly affect the cost. Decisions need to be made as to how much information must be on-line in disk storage and how much can be archived on tape. Retention times for much information may be dictated by law but there may be options for other data.

Data proliferation

This is a problem that is often difficult to control, in that initially the reaction is to computerize all the data possible. This can rapidly lead to a database of monstrous proportions. For certain data it may be more effective to use computerized records as flags for existing paper files that are seldom used. Procedures for eliminating out of date or dumping historical information to tape files are also needed. Generally a major point of contention among users is what data will be computerized and what will not.

Again, we come back to the need for user discussions and careful planning to finalize the database contents.

Performance

Requests for data by users must be satisfied with the speed appropriate to the usage of the data. The requirements of an epidemiological study may be less time-restrictive than those of a clinic carrying out an emergency care function or doing periodic health exams. A system which has a two-day turnaround is obviously insufficient for routine daily requirements yet may be fine for research applications. The requirement at another company may be only for weekly or monthly reports. The frequency of use of the data then will tell you how the software must perform as well as what the hardware requirements will be to provide adequate service.

Accuracy

Programs for edit checking must be incorporated into the data input system. It is difficult to correct data once it becomes part of the database. Therefore the onus is on the input system to ensure the data are as accurate as possible.

Security

This requirement is crucial in keeping with the confidentiality of medical records. Unfortunately, as we are finding out, computers are not entirely secure. There are two security issues that should be considered. The first being protection from unauthorized access to the database, and the second being the restriction of data within the system, that is some users may not have clearance to view or alter all of the data.

Maintenance of database integrity

The fulfillment of this requirement ensures that the database will not be damaged by any type of catastrophe. As with any computer system this is best done by maintaining a constant journal file which essentially carries a copy of the database with the changes, deletions or additions that are made. Daily backups also protect against accidental loss. A tape record of the database held in a separate facility from that of the computer is also a good method.

The implementation strategy

As a result of our three-year efforts, we have arrived at a philosophy for designing and implementing occupational health information systems. Data management is specific to every organizational environment! Decisions can only be realistically made by the users themselves.

With the use of generalized database management tools, and a plan for determining what data is important, who is responsible for it, and how it can be organized and used, every organization can produce an occupational health information system that is perfectly tailored to their own needs and operations.

Our cumulative experience has shown us that although we had good computerized tools, our implementation could have been made more efficient through the use of structured analysis techniques that are now widely used for computer project planning and management.

As the focus of this talk is not to discuss these techniques, I will simply mention a couple that have had wide success, especially in the areas of occupational health information systems. They are:

1. Structured Analysis Design Technique (SADT)

2. A Proprietary Technique of Softech Inc. in Massachusetts and Structured Analysis and System Specification by Tom Demarco.

Another major result of our efforts at Dofasco and Inco has been the launching of an Occupational Health Information System Product by the company that provided us with the DBMS, SIR Inc. The product is a health monitoring system which is fundamentally grounded in our philosophy of user driven system by providing each site with the tools that they need to develop a system, a framework, or model, that can be drawn upon and even directly used where applicable, and an implementation strategy that can be followed by the site themselves, or with the guidance of an occupational health information consultant. A subsequent development that arose from our design and development process is the integration of microcomputers into the overall structure, to provide distributed data entry and retrieval facilities. This will minimize the utilization of a central mainframe computer and allow organizations that are themselves geographically distributed to have a cost-effective means of using an occupational health information system. There are strong indications that distributed processing through micros will be the norm in the not too distant future.

To summarize then our experience

Having devoted considerable effort to the development of our Occupational Health Information System, we feel that:

It is more logical to build from the ground up with good tools and appropriate models than to remodel existing structures.

The Occupational Health Information System must ultimately come from the users themselves - designed to accommodate all of their needs; and that

The Occupational Health Information System must ultimately be used and maintained by the users themselves.

COMPUTER BASED INFORMATION SYSTEM FOR UNPUBLISHED LITERATURE

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Abstract

In conjunction with its rulemaking and staff support functions, the Occupational Safety and Health Administration of the U.S. Dept. of Labor has developed a computerized microfiche-based information storage and retrieval system. This system, named TIRS (Technical Information Retrieval System), contains contractor reports, results of consultant investigations, and other unpublished literature which have been microfilmed, indexed and stored in an Access Corporation System M. Detailed toxicological and economic studies, available exclusively from OSHA's docket files, are accessible through the TIRS. In addition, selected microfiche reports from the National Technical Information Service (NTIS) and the CIS (International Occupational Information Center) are retrievable by keyword search in minutes using the Hewlett Packard 1000 minicomputer and Access software developed specifically for OSHA. Future editions of the system have been planned to include foreign article translations and on-line catalog to the holdings of the Technical Data Center. Dial-up capability for OSHA's regional offices is contemplated. Present means for accessing this information resource by the medical community will be addressed.

Résumé

A l'aide de ses fonctions de réglementation et de soutien du personnel, l'Occupational Safety and Health Administration, du ministère du Travail des Etats-Unis, a mis au point un système informatisé, et basé sur microfiches, de mémorisation et d'extraction de l'information. Ce système, désigné TIRS (Technical Information Retrieval System), contient des rapports de contractants, des résultats d'études d'experts-conseils et autre documentation inédite, qui ont été mis sur microfiches, indexés et mémorisés dans un Access Corporation System M. Des études toxicologiques et économiques détaillées, disponibles

exclusivement dans les dossiers de fiches de l'OSHA, peuvent être consultées à l'aide du TIRS. De plus, des rapports choisis sur microfiches, du National Technical Information Service (NTIS) et du CIS (International Occupational Information Center), peuvent être extraits en quelques minutes par recherche au moyen d'un mot-clé, en utilisant le miniordinateur Hewlett Packard 1000 et le logiciel Access mis au point spécialement pour l'OSHA. Des modèles futurs de ce système doivent contenir des traductions d'articles étrangers ainsi qu'un catalogue pour la consultation directe des données du Technical Data Center. La possibilité d'appel de l'ordinateur par cadran est étudiée pour les bureaux régionaux de l'OSHA. Les moyens actuels visant à rendre cette source d'information accessible à la collectivité médicale seront traités.

Introduction

The process of Federal Regulation generates an enormous amount of information and paper. In most U.S. Agencies this paper is relegated to darker corners of the office or the file storage area. No attempt is made to index this information or make it more accessible to the public, although most of this paper was generated through agency efforts to involve the public. In the OSHA Technical Data Center a different approach was taken: All rulemaking papers traditionally relegated to the Federal Archives Center are being indexed and microfilmed.

The need for a computerized information system in the Technical Data Center became apparent around 1977. The rapidly increasing volume of paper materials and the increased demand for access to these materials became an acute problem. At the conclusion of a two-year research effort by OSHA staff and a private consultant, it was proposed that control of and access to the assembled information would best be obtained through the incorporation of an automated microfiche storage and retrieval system.

The purpose of this research was to investigate available system alternatives and to justify the cost of expanding to a fully automated system. Other considerations included: 1. space management, 2. growth factors, 3. file security and integrity, 4. reproduction time, 5. reproduction costs, 6. misfile costs, 7. file maintenance, 8. mailing costs, 9. document retrieval, 10. user benefits, 11. retrieval time, 12. filing time, 13. condition of documents, and 14. indexing.

Examples of each of these considerations can be illustrated in the following manner:

Space

Problem: The original docket office operation occupied 1,443 sq. ft., accommodating four full-time staff members, a reading room, and reproduction facilities. Files occupied 350 sq. ft.

Solution: Microfiche. An automated storage and retrieval system can house microfiche for all docket files in 47 sq. ft. Total space saved is 303 sq. ft.

Growth

Problem: Original System. Docket files increased at a rate of over one drawer per week or ten file cabinets per year requiring 70 sq. ft. of additional floor space per year.

Solution: Microfiche. The system mentioned previously provides room for may years growth; additional storage units can be acquired as necessary.

File security and integrity

Problem: Original system. Public access to files led to theft and misfiling of parts of legal record. Some old files existed only in the Docket Office. This could have been controlled by acquiring locked files and hiring extra personnel to monitor files and handle requests.

Solution: Microfiche. Duplicate fiche or paper copies from fiche will be provided. Original fiche inaccessible to public. Single pages cannot be misplaced on a 98-page fiche. Integrity and security are preserved.

Reproduction time

Problem: Original system. To copy a 98-page document required up to 45 minutes and demanded the constant attention of the staff.

Solution: Microfiche. A 98-page document requires less than five minutes. Once the Xerox 970 Microfiche Printing System is programmed, the operator may leave and continue other tasks. The time saving alone exceeds 2,000 hours per year.

Reproduction costs

Problem: Original System. 330,000 pages per year cost approximately $10,000 to reproduce on paper.

Solution: Microfiche. 330,000 pages in 98 image formate microfiche costs $336.73. Total savings per year is $9,630.61.

Misfile costs

Problem: Original System. The National Archives record service (NARS) File Operation Handbook states, "for 1964, the average file contained 3% misfiles, costing $60.00 per misfile per year." By applying this percentage rate and dollar figure to the system at an average of 10 pages per document misfiled, it would cost $81,000. NARS placed the 1981 cost at $120 per misfile.

Solution: Microfiche. Misfiles are virtually eliminated in the automated storage device.

File maintenance

Problem: Original system. A 1975 study conducted by the Social Security Administration indicated that the maintenance cost of hard copy materials was 11¢ per page. At this rate, the 450,000 pages to be filmed initially cost $49,500 to maintain and each new year's material (112,000 pages) an additional $12,320.

Solution: Microfiche. An additional technical person (GS-5/7) may be needed, but storage and space costs will be reduced as previously noted.

Mailing costs

Problem: Original system. A standard transcript (300 pages) costs $2.40 to mail.

Solution: Microfiche. Standard transcript costs 20¢ to mail.

Document retrieval

Problem: Original system. Retrieval by consulting Master Index, if available, or by trial and error.

Solution: Microfiche. Access number gives document type, category. Master List does not always have to be consulted.

Retrieval time

Problem: Original system. Up to 30 minutes.

Solution: Microfiche. Machine retrieval system requires approximately seven seconds.

User Benefits

Problem: Original system. Chronic backlog of two weeks for filling requests. User time spent searching unfamiliar files. Waiting time to use copying machine led to theft.

Solution: Microfiche. Five minute response time; choice of fiche or hard copy; less frustration and dissatisfaction.

Filing Time

Problem: Original system. Staff spent 14 hours per week (over 700 hrs. yearly) filing and refiling documents.

Solution: Microfiche. In automated storage - 30 minutes per week refiling time, saving 700 hours per year.

Condition of record documents

Problem: Original system. Hard copy presented problems of wear and tear on documents in frequent use.

Solution: Microfiche. Originals are kept in archives, inexpensive copy used for reproduction.

Indexing

Problem: Original system. None.

Solution: Microfiche. Indexing and a process controller would provide free text access.

There were two areas of information retrieval that presented the greatest concern. These were the Docket Office files and the existing microfiche files.

The Docket Office was the most chronic. The function of the Docket Office is to house as record information all documents that go into the making of an OSHA regulation or standard. It is the point of contact for public and freedom of information requests, as well as source material for cases in which litigation is necessary. In less than six years of operations, the Docket Office has expanded from one docket file to ninety-six.

OSHA assigns each developing regulation to a Project Officer, who assembles relevant studies, reports, comments, etc. and submits them to the official docket as OSHA's submittal to the record. Before the new system was implemented the project officer was the key to the docket contents.

The second area of concern was the existing microfiche files. These microfiche numbered well over 100,000. These files included fiche from the National Technical Information Service (NTIS), National Institute for Occupational Safety and Health (NIOSH), U.S. Bureau of Mines, Center for International Occupational Safety and Health (CIS), and microfiche editions of the Federal Register and Code of Federal Regulations. Retrieval of these microfiche could only be provided when users had the accession number. Because the number of microfiche was so great, it was nearly impossible to make and maintain a proper inventory. The microfiche were filed by accession number in a

Data Elements	Key	Length of Rec.		NTIS	CIS	Dock.	Card Cat.
		Min.	Max.				
Accession Number	Y	2	20	X	X	X	X
Document/Category/Type	Y	2	5			X	
Organization/Publisher	Y	2	60				X
Author #1	Y	2	50	X	X	X	X
Author #2	Y	2	50	X	X	X	X
Item #1	Y	2	40	X	X	X	X
Item #2	Y	2	40	X	X	X	X
Item #3	Y	2	40	X	X	X	X
Item #4	Y	2	40	X	X	X	X
Item #5	Y	2	40	X	X	X	X
Item #6	Y	2	40	X	X	X	X
Item #7	Y	2	40	X	X	X	X
Item #8	Y	2	40	X	X	X	X
Item #9	Y	2	40	X	X	X	X
Item #10	Y	2	40	X	X	X	X
Title #1	N	2	60				X
Title #2	N	2	60				X
Title #3	N	2	60				X
Title #4	N	2	60				X
Year of Publication	Y	4	4	X	X		X
File Name	Y	4	4	X	X	X	X
Date Filmed	N	6	6	X	X	X	
Access Entry Date	Y	6	6	X	X	X	X
Fiche/Frame/Cont'd.	N	2	15	X	X	X	
Access Code	Y	7	7	X	X	X	
Comments #1	N	2	60	X	X	X	X
Comments #2	N	2	60	X	X	X	X
Total Characters per Data Record per File Type				663	663	685	1074

TABLE 1: List of Data Elements

totally manual system. The probability of misfiles was high. Valuable information contained within these various files was often unavailable because no search capability existed.

The ability of the system to respond favorably to user inquiries depended upon the development of a suitable file structure. Types of information found in each file plus types of information most often requested by users (scientists, lawyers, engineers) were assembled and certain commonalities were extracted. These commonalities were refined into the data elements which comprise each file in the system. (See list of data elements, page following). It follows that certain data elements become suitable indexing elements. Indexing is performed by contract personnel.

The information contained in the rulemaking record is submitted to the Docket Office in response to various milestones along the regulatory pathway. (See Appendix A.) Basically, the document submitted will be in response to some action taken by OSHA; i.e. Advanced Notice of Proposed Rulemaking or Notice of Hearing. These are the kinds of factors which determine how a document is labelled once it is generated or received by OSHA.

Until the decision was made to utilize an automated storage and retrieval system with microfiche as the storage medium and a mini-computer, with key-word search, providing the retrieval capability, vast quantities of unpublished and published information lay virtually untapped; filed away in a file drawer with only a typed master list as the key to its contents.

The research effort led to the selection of a system designed, manufactured and marketed by Access Corporation, Cincinnati, Ohio. Access manufactures the storage device and custom develops the software. The computer and peripheral equipment are Hewlett-Packard, marketed under special agreement by Access. The equipment may be categorized as belonging to one of two units, or subsystems. The System M, and the controller, or IDCS (Integrated Document Control System).

System M comprises the storage module, the buffer, and the on-line console. With this subsystem, one can store and retrieve microfiche providing there is a carefully maintained index of fiche and carrier numbers. The storage module contains drawer-like cartridges which contain the coded Mylar carriers holding microfiche. Upon command (Search) from the console, the proper carrier is located and extended to the operator. The buffer holds carriers to be re-filed. This unit is searched simultaneously with the M module.

The IDCS is the name applied to the controller/software subsystem, and comprises the computer, disc drive, tape drive, system console, 2 printer terminals, and a system printer. The IDCS Software, specifically tailored to OSHA's system requirements, make the turnkey package workable. (See Appendix B for equipment specifications).

TDC staff and Access systems analysts worked closely in the development of our file structure. The software was put together by using a combination of off-the-shelf modules as well as specially written programs. Some of our requirements were different from others that had been purchased. For example, TDC wanted to have the ability to control the assignment of microfiche to a particular carrier in the M storage device. To accommodate this request, Access rewrote a program so that TDC could have access address control rather than it being computer assigned by the process controller.

IDCS is a turnkey operation that allows users to search for particular records through keyword accession. Keyword accessions can be accomplished by using single words, phrases, or multiple values. When a user enters a term that is specific to some type of subject matter, the indexing program in the process controller looks at all records that have a value equal to the term that was entered. The results (hits) are displayed on a CRT. The user can then expand or contract the search by using Boolean search logic with other terms to limit the results. Once the user achieves satisfactory results, he can tell the system to pull the document(s) on microfiche from the M unit.

The user can request a paper copy or a microfiche copy of the documents he has just searched. Either kind of copy can be produced at a minimal expense.

TIRS, as currently structured, has a 14 field display of information per record. These fields include: 1. Accession Number, 2. Master List Item Number, 3. Category/Document Type, 4. Publisher, 5. Author, 6. Item, 7. Title, 8. Year Published, 9. File Name, 10. Date Filmed, 11. Fiche/Frame/Continued, 12. Status Codes, 13. Comments, and 14. Access Address.

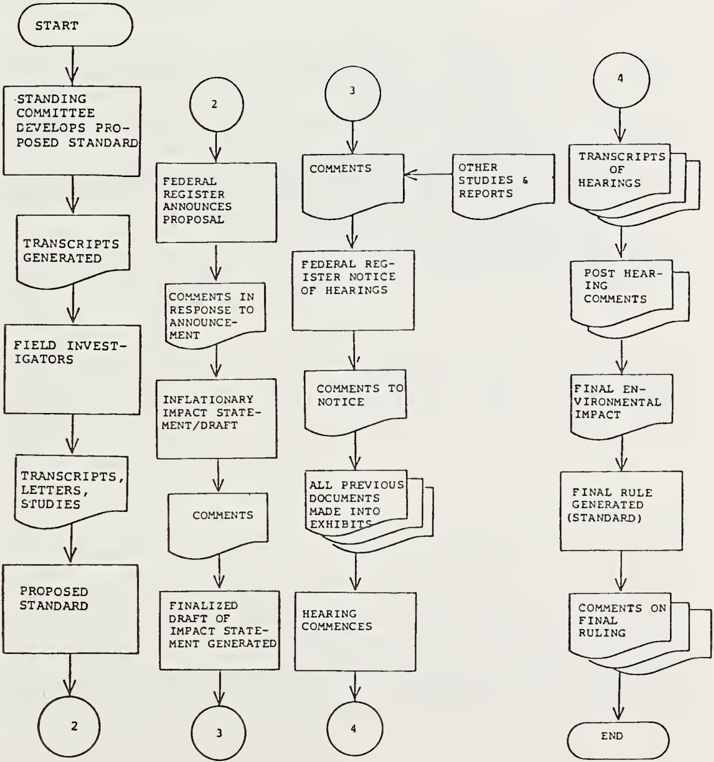
All of these fields are not searchable. The fields such as a "Title" and "Comments" display information in a format that is purely informational to the user. It helps to define or explain other things about the record being recalled. However, the record is still searchable and usable without these fields.

The beauty of OSHA's system lies in two distinct characteristics: its unique blending of source document storage with an on-line information data base, as well as in its potential for expansion. The varieties of information, once converted to microfiche, applicable to this system are numerous. OSHA is presently combining regulatory files, government publications and a library card catalog in one system. Other types of files can be added as needs change.

The potential exists for future expansion. The system will support up to eight disc drives and up to sixteen M units, at transmission rates of up to 2400 baud. OSHA can therefore, greatly expand the system and incorporate its Regional and Area Offices by dial-up access. This system may eventually be accessible to state and local governments, unions and scientific organizations and the general public.

APPENDIX A

PRESENT SYSTEM FOR STANDARD FORMULATION


START
STANDING COMMITTEE DEVELOPS PROPOSED STANDARD
TRANSCRIPTS GENERATED
FIELD INVESTIGATORS
TRANSCRIPTS, LETTERS, STUDIES
PROPOSED STANDARD
2
2
FEDERAL REGISTER ANNOUNCES PROPOSAL
COMMENTS IN RESPONSE TO ANNOUNCEMENT
INFLATIONARY IMPACT STATEMENT/DRAFT
COMMENTS
FINALIZED DRAFT OF IMPACT STATEMENT GENERATED
3
3
COMMENTS
OTHER STUDIES & REPORTS
FEDERAL REGISTER NOTICE OF HEARINGS
COMMENTS TO NOTICE
ALL PREVIOUS DOCUMENTS MADE INTO EXHIBITS
HEARING COMMENCES
4
4
TRANSCRIPTS OF HEARINGS
POST HEARING COMMENTS
FINAL ENVIRONMENTAL IMPACT
FINAL RULE GENERATED (STANDARD)
COMMENTS ON FINAL RULING
END

APPENDIX B

A. Access Corporation System CCM Model 860 includes:

1. Main Module
2. Two buffer selectors
3. Two consoles
4. One coder
5. Mylar carriers (200% verification for pre-coding)

B. Hewlett-Packard HP-1000 minicomputer model 2176C, I series includes:

1. Central Processing Unit
    a. Core memory - 512 kilobytes
    b. 16-channel asynchronous multiplexor-supports 30 terminals
    c. RS232 Interface
    d. I/O Data transfers-up to 2.28 million bytes per second
    e. Operating system-HP RTE IV B
2. Master disc drive and controller - 120 megabytes
3. Master tape drive and controller - 1600 bytes per inch
4. Line Printer - 180 characters per second
5. HP 262IP CRT printer terminals
6. HP 2645 system console.

OCCUPATIONAL HEALTH INFORMATION SYSTEMS - FUNCTIONAL REQUIREMENTS AND DESIGN ISSUES

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Flow General Inc.
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Abstract

A comprehensive occupational health information system supports the daily information needs of medical staff members and of industrial hygiene and safety specialists. It also should meet the long-term information needs of corporate managers and legal staffs who may be called upon years in the future to defend the ways in which employees have been protected against workplace hazards. These comprehensive information systems provide for the storage, analysis, retrieval and reporting of employee medical record data, workplace monitoring data and detailed environmental agent information.

Occupational health information should provide printed schedules, government-mandated reports, intra-company reports on individuals and designated groups of employees and work-places, responses to on-line queries and statistical analyses and reports for special studies.

Each essential function, including scheduling, medical surveillance, industrial hygiene surveillance and analysis and reporting, involves special input, processing and output. Essential features include modifiable file and record structures, standard coding schemes, data editing under user-specified criteria, interfaces to other corporate computer systems, comprehensive statistical capabilities and sophisticated data security.

Résumé

Un vaste système de renseignements sur la santé professionnelle fournit les renseignements quotidiens nécessaires aux membres du personnel médical, de l'hygiène industrielle ainsi qu'aux spécialistes de la sécurité. Il doit également satisfaire aux besoins de renseignements à long terme des gestionnaires du secteur privé et du personnel juridique à qui il pourra être demandé ultérieurement de défendre la façon dont les employés ont été protégés contre les dangers du milieu du travail. Ces vastes systèmes de renseignements doivent pouvoir emmagasiner, analyser, retrouver et donner un compte-rendu des données du dossier médical d'un employé, des

données de contrôle du milieu de travail ainsi que les renseignements détaillés sur les agents environnementaux.

Les renseignements sur la santé professionnelle doivent fournir des horaires imprimés, des rapports commandés par les gouvernements, des rapports internes de la compagnie concernant les personnes et les groupes désignés d'employés ainsi que les milieux de travail, des réponses aux interrogations directes et analyses statistiques de même qu'aux rapports sur des études spéciales.

Chaque fonction essentielle, y compris la programmation, le contrôle médical, le contrôle d'hygiène industrielle ainsi que l'analyse et les comptes-rendus, comportent des entrées, des traitements et des sorties spéciaux. Les caractéristiques essentielles comprennent des fichiers et des structures de dossiers modifiables, des profils de codifications normalisés, une édition de données conformes aux critères exigés par l'utilisateur, la communication avec d'autres systèmes d'informatique du secteur privé, une capacité statistique complète et une protection sécuritaire avancée des données.

Introduction

Functional Requirements and Design Issues for Occupational Health Information Systems are conclusions resulting from more than 10 years spent analyzing, evaluating, designing, and developing medical information systems by myself and my colleagues. During the last year we have designed and developed a computerized Occupational Health Information System called FLOW GEMINI that incorporates functions and features described here.

I believe that whether you represent a large or small organization, develop your own system or evaluate commercially available ones, these functional requirements and design issues are completely relevant.

My talk is divided into three parts. First, an overview of requirements and functions from both a user and computer system perspective. Then, specific data and functions required for a comprehensive occupational health system. And, finally, what I see as essential features and tasks for a truly flexible and operationally acceptable occupational health system.

An overview

Companies adopt computerized occupational health systems for many reasons. But the reasons generally fall into one or more of the four categories shown on Figure 1.

Legal compliance is a motive for computerization because vast amounts of data must be maintained and reported to comply with national and other governmental laws and regulations. The major computer functions associated with legal compliance are storage of the data and its subsequent reporting. Analysis and retrieval are involved but are less dominant functions.

	STORAGE	ANALYSIS	RETRIEVAL	REPORTING
Legal Compliance	×			×
Legal Protection	×		×	
Reducing Health Risks		×	×	
Facilitating Research		×	×	

Figure 1: Rationale and Computer Functions

Legal protection of the organization is an increasingly important motive in computerizing occupational health data. When data are stored in a computer, it is much more consistently gathered and stored and is usually more accurate. Moreover, it is infinitely easier to retrieve in the case of litigation.

Health risks are reduced when data are available for computerized analysis and retrieval because there is a much greater probability of early detection of adverse health effects from exposure to hazardous agents.

And finally, epidemiological and toxicological research are virtually impossible without a computerized system for the analysis and retrieval of employee work history, exposure and medical exam data.

An occupational health information system has two major functions in any organization: monitoring the health of the employees and monitoring the conditions in the workplace (Figure 2).

Several types of input records are required to monitor employee health and workplace conditions. First, personnel records. Clearly, up-to-date work history and demographic data must be maintained for each employee. And of course, medical record data must be available from the Medical Department, and information on personal protective devices should be in the employee's record.

For workplace monitoring, Industrial Hygiene and Safety Departments need to provide incident and monitoring data, and up-to-date purchasing and inventory records must be maintained for all potentially hazardous environmental agents in the workplace.

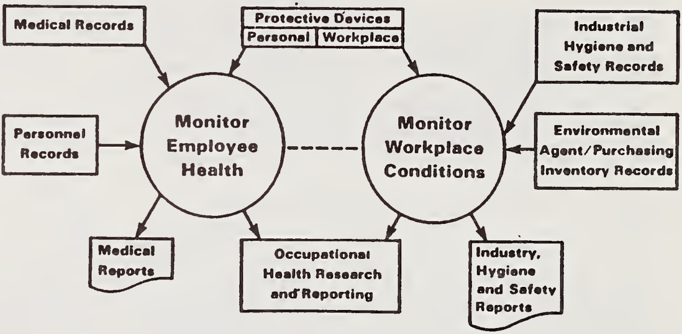
Medical Records
Protective Devices
Personal
Workplace
Industrial Hygiene and Safety Records
Personnel Records
Monitor Employee Health
Monitor Workplace Conditions
Environmental Agent/Purchasing Inventory Records
Medical Reports
Occupational Health Research and Reporting
Industry, Hygiene and Safety Reports

Figure 2: Overview of an Occupational Health Information System

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Last there is the output - the ultimate value of any information system derives from the analysis and retrieval of its data. The system should provide essential information to those responsible for complying with the law, protecting the company and its workers and doing research. A potentially infinite number of reports and analyses are needed for the Medical, Industrial Hygiene and Safety Departments and for management and research staffs.

Clearly, maintaining an up-to-date, comprehensive, occupational health system demands cooperation and linkage with many groups outside the medical, industrial hygiene and safety departments (Figure 3). Personnel, inventory, and manufacturing and administration are inevitably involved because links are required to their manual or automated systems of information. An occupational health system contains employee data, but this must be updated with personnel changes such as transfers, new hires, etc. It contains data on workplaces, but workplace data change when there are changes in manufacturing. Similarly, inventories change in conjunction with manufacturing changes, and environmental agent locations and exposures change accordingly.

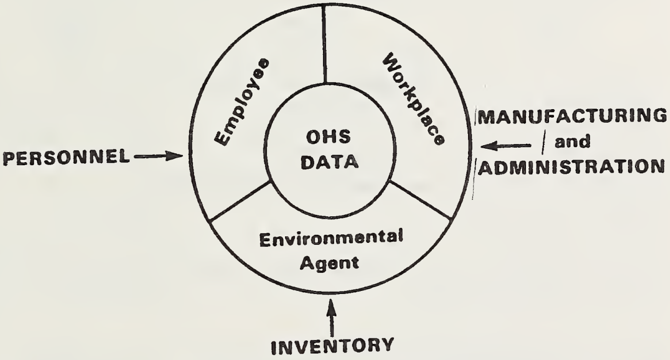

Figure 3: Required Data Base Linkages

Required data and functions

A comprehensive occupational health system must incorporate a great many types of data and perform numerous and very specific functions. I'd like to briefly review these requirements.

While specific data items will vary somewhat from company to company and industry to industry, there always must be records pertaining to employees, to workplaces and to environmental agents - most frequently the chemicals and materials used in manufacturing.

Employee data include appropriate demographic items, health and work history, medical exam and associated data, injury and illness details, reasons for mortality, results of industrial hygiene sampling, records of safety and health training, and pertinent details concerning assigned protective devices.

For the workplace, a description of the workplace itself, area sampling results, an identification of protective devices within the work location, accident and spill details, and an identification of environmental agents in the workplace are all required.

EMPLOYEE	WORKPLACE	ENVIRONMENTAL AGENT
Demographic	Description	Description
Health History	Area Sampling	Hygiene Information
Work History	Protective Devices	Physical Properties
Medical Exams	Accidents	Personal Protection
Lab Tests	Environmental Agents	Health Hazard
Injuries and Illnesses		Ingredients
Mortality		Spill Procedures
Personal Sampling		Precautions
Safety and Health Training		Transportation
Protective Devices		

Figure 4: Required Occupational Health Data

The environmental agent data are very similar to those required for material safety data sheets. They include descriptive information about the agent and its supplier, hygiene information, physical property and personal protection details, health hazard data, ingredients, spill procedures and precautions, and finally transportation information.

All items of employee, workplace, and environmental agent data should be capable of interrelationship. Employees work in specific work locations and perform specific jobs, using one or more environmental agents. An occupational health system must be able to tie together all items of information related to an individual's unique exposure history and health status. In computer jargon, a relational data base capability is essential.

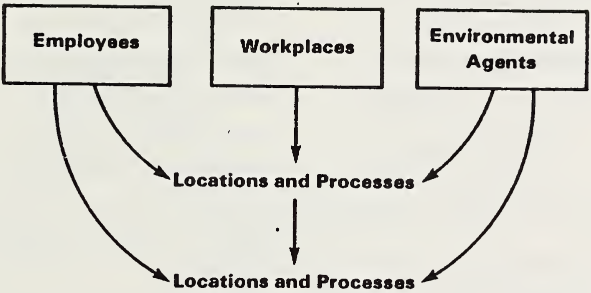

Figure 5: Required Data Relationships

Medical and industrial hygiene surveillance are the cornerstones of any comprehensive occupational health system (Figure 6). These inevitably involve scheduling mandated medical exams and sampling. Some form of automated scheduling is therefore highly desirable. Retrieval, analysis, and reporting are of course part of the surveillance functions. However, they should also be separate tools within the information system so they can be used for new applications in the future.

- Medical and Industrial Hygiene Surveillance
- Scheduling
- Retrieval, Analysis and Reporting

Figure 6: Essential Functions

Now let's look at each of these functions in somewhat more detail.

MAJOR INPUTS	MAJOR OUTPUTS
Health History	Medical Record Report
	Medical Problem Report
Work History	Hearing Report
	Exam Results to Employees
Exam Findings	-------------------------
Lab Results	Department, Plant, Company Summaries
	Government Reports
Accident Reports	

Figure 7: Medical Surveillance

In Figure 4 we looked at the major types of employee data within a comprehensive occupational health system. In Figure 7 we see how input data relate to output reports needed for medical surveillance.

Reports should be available for both individual employees and exposure-related groups. This is the purpose of the broken line separating the examples of medical reports.

A report that includes recent medical record data for any given employee is essential. It is also important to highlight an individual's potential medical problems. Most governments require a hearing conservation program for employees exposed to high levels of noise, and these same governmental groups often require that results of hearing and other exams be made available to employees. These are some of the most commonly required reports related to individual employees.

Group reports of out-of-range results for employees within a given exposure-related group or specific departments or plants within a company provide the first steps in identifying potential adverse health effects and controlling risks within the organization.

MAJOR INPUTS	MAJOR OUTPUTS
Personal Sampling Results	Personal Sampling Report
Area Sampling Results	Area Sampling Report
Environmental Agent Inventory Data	Industrial Hygiene Problems
	Employee Work and Exposure History
Environmental Agent Physical, Health, Hygiene and Transportation Data	Environmental Agent Inventory Report

Figure 8: Industrial Hygiene Surveillance

Individual and summary reports are as important to industrial hygiene surveillance (Figure 8) as they are to medical surveillance. A comprehensive occupational health system provides personal and area sampling results, identifies exposure problems and provides a complete work and exposure history for each plant employee as well as an inventory of all environmental agents.

Schedules showing what employees, work locations or protective devices are due for an exam or inspection are a natural adjunct to surveillance reports (Figure 9). Reminders about exams that are due or overdue and a capability for on-demand, completely up-to-date information about who and what is scheduled are extremely useful in any plants, and the larger the work force and workplace the more important computerized scheduling support becomes.

MAJOR INPUTS	MAJOR OUTPUTS
Identification of Entity and Exam/Inspection	Daily, Weekly, Monthly Schedules
Date and Time or Interval of Exam	Reminders
On-line Queries	"Scheduled" Flags in Data Base

Figure 9: Scheduling

- Modifiable Standard Reports
- User-defined Reports
- On-line Query Capability
- Statistical Package

Figure 10: Retrieval, Analysis and Reporting Requirements

Corporate and governmental requirements for reporting, retrieval, and analysis are constantly modified in the dynamic occupational health system (Figure 10). These so-called standard reports should be capable of easy modification. Inevitably, new requirements from government agencies as well as corporate management also mean that new reports must be developed, ideally by noncomputer personnel. Not all capabilities can be anticipated at the time of system implementation and not all requirements lend themselves to standardized reports. Therefore, an on-line query capability is essential. This allows professionals who know little about computers to retrieve specified data. And finally, for research staffs, a sophisticated statistical capability is essential for analyzing a growing data base.

Essential features and tasks

There are certain essential features and tasks associated with implementing a flexible and comprehensive occupational health information system, no matter what the nation or industry and regardless of whether you are going to develop a system or purchase a commercially available system.

- Modifiable and Expandable Data Base
- Standard Coding Schemes
- Comprehensive Data Entry and Editing System
- Modifiable Reports
- Interface to Other Corporate Systems
- Confidentiality and Security
    - functional access control
    - data base access control
    - physical security and backup

Figure 11: Essential Features

Because of the dynamic nature of the occupational health field, it is essential that the structure and contents of any predefined data base be easily modifiable and expandable by the user. A company that buys a system should not have to go back to the vendor to change the structure and contents of a data base. They should be able to do it themselves.

The fields of occupational medicine and industrial hygiene are constantly changing, yet there is a need to aggregate, classify and analyze data. This means that standard coding schemes such as ICD-9 should be available.

The accuracy of data is paramount, and a comprehensive data entry and editing system must be in place for editing and validating all data that is entered into the system.

To meet new and changing reporting requirements, standard reports should be modifiable, again independent of a vendor or data processing professionals if possible.

Personnel, inventory, and other corporate information systems must provide regular updates to the OHS.

And, finally, confidentiality and security are critical. Not everyone should be able to modify records, restructure the data base, or assign passwords. This means that several levels of functional access within the system are important.

Controlling access to data on a need-to-know basis is another important security feature. Industrial hygienists don't need to have access to medical data, and there usually is little reason for a physician at one plant to be able to access routinely the medical data for employees at another plant. There should be the capability, however, for corporate level medical staff members to access data from all plants for research and reporting.

- Workplace Definition and Job Coding
- Environmental Agent Inventory
- Administrative Maintenance Procedures

Figure 12: Essential Tasks

The most advanced form of data security is provided by the process of data encryption, a technique originally developed for the security of military data. Physical security and back-up capabilities are probably more important with medical information systems than almost any other. It is extremely important to log all changes that are made to the data so that there can be a complete reconstruction in the case of computer or administrative problems.

When implementing any complex new system, there are many preparatory tasks (Figure 12). Many companies have considerable work to do in preparing for a fully integrated and comprehensive occupational health system although, fortunately, computerization does not have to be postponed until all these tasks are completed. Workplaces need to be defined and surveyed; jobs must be coded, preferably based on or related to exposure; and there must be an inventory to determine what environmental agents are present in each plant, where the agents are located, and who is using them. Finally, procedures must be defined and implemented for regularly maintaining all of this information and providing updates at appropriate intervals. This, of course, involves interfacing and planning with the several non-occupational health departments referred to earlier.

THEME IV

CURRENT OCCUPATIONAL HEALTH PROBLEMS IN THE CHEMICAL INDUSTRY

PROBLEMES COURANTS DE SANTE PROFESSIONNELLE DANS L'INDUSTRIE CHIMIQUE

CURRENT OCCUPATIONAL HEALTH PROBLEMS IN THE CHEMICAL INDUSTRY

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The demonstration of liver angiosarcoma from long-term exposure to vinyl chloride raised concerns about the whole spectrum of subtle long-term health effects from the exposure to chemical agents in the workplace. Current occupational health problems include the development of occupationally-related cancers, reproductive effects, pneumoconioses, chronic non-malignant respiratory diseases, heart diseases, haematological disorders, neurological diseases, behavioural disorders, disorders commonly referred to as stress-related effects, and renal diseases. Many of these diseases demonstrate a long latent interval between first exposure on the job and appearance of the disease. Many are related to non-occupational factors such as cigarette smoking and aging. The demonstration of a causal relationship between these chronic diseases and occupational exposure is difficult and often surrounded by controversy. There is need for epidemiological studies based on adequate documentation of workplace exposures and employment history, and the relationship of these to the health effects under study. Professor Doctor A.M. Thiess, MEDICHEM Chairman referred to this in his opening remarks to this Congress.

In approaching my review it became obvious to me that I could not deal with all the current occupational health concerns. Therefore, I have decided to concentrate my review on neurotoxicity, behavioural disorders, nephrotoxicity, along with a few general comments on occupational cancer, reproductive hazards and alcohol intolerance.

Neurotoxicity

Neurotoxic effects may be brought about by a wide variety of chemical agents. These agents may produce their effects by the following methods:

1. Agents causing hypoxia e.g., carbon monoxide

2. Agents with a reactive neurotoxic intermediate e.g., n-hexane

3. Agents which accumulate in the body and exert neurotoxic effects e.g., mercury, lead

Neurotoxic effects from metals and metal compounds

Many metals and metal compounds are capable of producing neurological effects in workers. Some of these neurological effects with paralysis have been known from antiquity. Neurotoxic effects from metals and metal compounds depend on :

1. Ability to penetrate into the nervous system. Swedish autoradiography studies show that Cd^{++} and Hg^{++} have a similar distribution immediately after administration. Later on, however, the distribution of Hg^{++} in the nervous system is evident.

   There are differences in the ability of specific compounds of mercury to penetrate the central nervous system and bring about neurological disease. Methyl mercury is more active than mercury vapour which in turn is more active than inorganic mercury compounds.

2. Selective uptake in neuro-anatomic structures. Methyl mercury is taken up in the subcortex producing visual impairment and in the cerebellum producing ataxia.

Mercury

Neurological disorders from exposure to mercury vapour and to mercury compounds were known to early occupational physicians. Depending on the degree of exposure, mercury vapour effects may be:

1. Mild - with fatigue, weakness and gastro-intestinal disturbances.

2. Moderate - with sensory disturbances including paresthesia of the extremities, tongue and around the lips.

3. Severe - with ataxia, constriction of the visual fields and personality changes.

Methyl mercury is particularly neurotoxic producing central nervous system effects in humans without peripheral effects. Rats, on the other hand, show peripheral effects at will. Methyl mercury readily penetrates the blood/brain barrier. It is accumulative and slowly eliminated, discovery of neurological effects following prolonged exposure, as in the Minamata cases, is unlikely. Complete recovery from acute short exposure is likely. Methyl mercury has a major effect in producing faulty development of the foetal brain.

Lead

As with mercury, neurological disorders from lead have been known for a long time. Depending on the form and degree of exposure, effects may be:

1. Mild - with fatigue, pallor, anemia, sleep disturbance and gastro-intestinal symptoms.

2. Moderate - with peripheral neuropathy ('wrist drop'). Lead directly affects the peripheral nerves. Seppalainen and Hernberg showed reduced motor conduction velocities (MCV) in the median and ulnar nerves when the blood lead concentration in workers exceeded 50 micrograms per 100 millilitres (50 µg/100 ml.).

3. Severe - with defective memory, irritability , ataxia, encephalopathy, coma and convulsions. Severe poisoning may be complicated by later intellectual impairment. Children are believed to be at greater risk.

Fatal cases with encephalopathy show cerebral edema, vascular changes with focal necrosis and a low average lead content of the brain. The lead content of the cortical gray matter and basal ganglia is increased.

The relationship of lead exposure to other neurological diseases e.g., amyotrophic lateral sclerosis (ALS) has been raised. ALS is associated with selective motor neuron degeneration. Ronnervi and Conradi reported higher levels of lead in the blood plasma and central nervous system of patients with ALS when compared to controls. In my opinion there is no causal association between occupational and/or environmental exposure to lead and these neurological diseases.

Organic lead compounds

Tetraethyl lead and tetramethyl lead are used in leaded gasoline. High acute exposure to TEL has produced acute psychosis with hallucinations. TEL was nicknamed 'looney gas' when it was first introduced for leading gasoline. TEL readily penetrates the blood/brain barrier. Its transformation is rapid.

Arsenic

Neuropathy is produced by exposure to arsenic compounds after short high exposure or repeated low exposures. Concentration of arsenic in the brain is low. Data on uptake by peripheral nerves has not been well documented.

Manganese

Long-term exposure in miners has been associated with Parkinson-type symptoms after two or more years of exposure. Symptoms include apathy, anorexia, monotonous speech with poor articulation, muscle rigidity, tremors, and gait disturbance. Chronic degenerative changes are found in the basal ganglia. Neonate brains and growing brains in experimental animals are more vulnerable. There is limited uptake of manganese by the brain but manganese has a long biological half-life.

Thallium

Accidental poisoning with thallium has occurred from its use as a pesticide. Symptoms of poisoning include muscle pain, muscle weakness, mental confusion, tremor, paresthesia, muscle atrophy, delerium and convulsions. Pathological studies show that the dorsal columns of the spinal cord are mainly affected. There is also destruction of the anterior horn cells. The thallium content of the brain is not high but it does penetrate the blood/brain barrier.

Tellurium

There is limited evidence of neurological effects in humans. Depression and amnesia have been reported in one study in which there was high exposure.

Selenium

Selenium is associated with 'blind staggers' in cattle and other domestic animals. This condition is believed to be due to the combination of selenium with some other, as yet unknown, factor. There is no evidence of human neurotoxicity.

Bismuth

High exposure to inorganic bismuth salts may cause tremors, gait disturbances, muscle cramps, and weakness. Bismuth is capable of crossing the blood/brain barrier. Organometallic bismuth (trimethyl bismuth) has been associated with ataxia, convulsions and encephalopathy in experimental animals.

Tin

No neurotoxic effects have been reported from occupational exposure to tin. A pharmaceutical agent, used for the treatment of acne, containing organotin compounds (diethyl-,diiodide, and triethyl-monoiodide, tin compounds) was found to have serious adverse health effects. Fatal cases showed cerebral edema and increased intracranial pressure.

Aluminium

Long term antacid therapy with aluminium hydroxide has resulted in phosphate depletion. The resultant changes in Ca^{++} balance has resulted in neuromuscular symptoms. Patients on renal dialysis with aluminium in the dialysate have developed 'dialysis encephalopathy'. Uremic patients retained aluminium in the brain. Some workers have attempted to implicate aluminium in the pathogenesis of Altzheimer disease. I do not believe there is any causal association.

Neurotoxic effects from organic compounds

A number of organic compounds including methyl n-butyl ketone (MNBK), n-hexane acrylamide and carbon disulphide have produced neurotoxic effects. These are chemically dissimilar but on prolonged exposure to low levels or short exposure to high levels they all cause the long large axones of the central and peripheral nervous system to undergo a progressive retrograde degeneration. These compounds or their metabolites inhibit brain and peripheral nerve glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and phosphofructokinase (PFK) two main enzymes involved in glycolysis. Fast axonal nerve conduction depends on ATP generated by glycolysis. 2,5-Hexanediol has been identified as the neurotoxic metabolite of n-hexane and MNBK. 2,5-Hexanediol applied locally to peripheral nerves produces giant axonal swelling whereas 2,4- or 1,6-Hexanediol do not produce this experimental lesion. Acetone, other ketones, and other C5 - C7 hydrocarbons do not produce this neurotoxic effect.

n-Hexane

On acute exposures to high levels n-hexane produces a narcotic effect. In 1969 Yamamura reported peripheral neuropathy in Japanese workers exposed to n-hexane. Similar reports appeared from the U.S.A., France and Italy. This neuropathy is associated with high occupational exposures - about 25 times the recommended airborne exposure limits. In addition, skin exposure with solvent soaked rags has been a factor. Cases of n-hexane neuropathy have also been reported in individuals engaged in 'glue-sniffing' (really 'solvent-sniffing'). Air concentrations in glue sniffing run about 40,000 to 50,000 parts per million in air (ppm). The solvents used in these adhesives commonly are mixtures of n-hexanes with ethyl acetate, xylene, methyl ethyl ketone, nitropropane, 2-heptanone, and acetone. The symptoms include symmetrical numbness of the fingers and toes, weakness, weight loss, difficulty in pinching, weakness, atrophy and occasionally blurring of vision. Position sense remains intact. Mild cases generally show complete recovery within ten months. Very severe cases never fully recover their full strength. The pathological picture shows paranodal giant axonal swelling with myelin retraction. The swelling contains many neuro-filaments of 10 micrometres in size.

Methyl n-butyl ketone

MNBK produces a similar effect through the same metabolite, 2,5-hexanediol. Cases were first reported in 1973 from the U.S. in fabric workers.

Other solvents

Reports of neuropathy associated with exposure to a number of organic solvents including acetone, methyl ethyl ketone, gasoline, etc, have appeared. Such reports have been viewed with skepticism. Good solvent analysis is necessary to rule out the presence of n-hexane as the causal factor.

Acrylamide

Acrylamide is a synthetic monomer used in making textiles, as an ingredient in groutings, etc.. The monomer is highly neurotoxic producing an encephaloneuropathy. Symptoms of over-exposure include rhinitis, sore throat, hallucinations, disorientation, ataxia, speech disturbances and later numbness and tingling in extremities, stocking/glove anaesthesia, and paralysis. Affected workers show excellent recovery on removal from exposure.

Solvent neuropathy

Antti-Piocha in Finland followed 106 workers reported to have neurological effects from solvent exposure from 1970 to 1974. These 106 workers were offered follow-up re-examination in 1978, of whom 87 were re-examined. The author could come to no general conclusion. There were great individual differences in the original response to solvents and the prognosis of the disease among individuals. Pederson and Rasmussen in 1982 looked for, but could not find, any haematological effects in workers exposed to solvents. The diagnosis of neurological effects must be based on the signs and symptoms of neurological involvement.

Neurotoxicity of polychlorinated biphenyl (PCB)

In 1968 about 1,000 cases were associated with the consumption of contaminated rice oil. The factory which produced the rice oil used PCB as a thermal conductor in a heating process to deodorize the oil. The PCB leaked out and contaminated the rice oil. The major effects among people using the contaminated oil were:

1. Skin - acneform rash and skin pigmentation

2. Eye - cheese-like discharge from Meibomian glands with visual disturbance

3. Neurological effects - with complaints of paresthesia of the leg, headache, hyperesthesia of legs (20%), and absent or diminished deep tendon reflexes (20%).

There were no central lesions involving brain, cerebellum or cranial nerves. There were no cases with paralysis.

Electro-encephalograms were normal. Motor conduction velocity tests showed slowing of the sural nerve conduction. Patients who showed health effects ingested an average of about 2 grams of PCB or 70 mg/day/kilogram.

Organophosphorus neurotoxicity

Organophosphorus compounds inhibit cholinesterase enzymes. Their acute toxic effects are related to the degree of inhibition. It has been found that some inhibited cholinesterases are capable of producing a delayed neurotoxic effect. In the 1930's there were about 10,000 cases of 'ginger jake paralysis' from the consumption of illicit spirits containing tri-o-cresyl phosphate (TOCP). In Morocco, cooking oil contaminated with TOCP was used in cooking in 1959. Many cases of peripheral neuropathy were associated with the use of this oil. The inhibited cholinesterase is aged and converted into a neurotoxic esterase which disrupts the normal metabolism of nerve tissue. Degeneration of this myelin sheath along long axones is noted. In cases where neuropathy occurs there is 70% - 80% inhibition of cholinesterases followed by a latent interval of 7 to 14 days.

Clioquinol neuropathy

In Japan about 9,000 cases of subacute myelo-optico-neuropathy (SMON) were associated with the use of clioquinol medication. The pathological examination showed degenerative changes in the pyramidal tract, optic nerve, posterior column of the spinal cord and the peripheral nerves. It is not known why this effect was produced at a specific time and only in Japan. It was suggested that the effect of clioquinol was related to some other environmental change but no such changes could be identified.

Behavioural disorders

Because the brain is the seat of emotional behaviour, concern has been expressed that chemicals which have neurotoxic effects may cause subtle and long term effects on the brain resulting in behaviour changes. Foa, et al., noted that chemicals may affect the central nervous system and thus affect behavior. These authors stress the need to develop procedures for the detection of less obvious but still destructive behavioural changes induced by long term exposure to low levels of certain chemical agents. In the review of neurotoxicity several references were made to agents which caused emotional and psychotic effects in cases of over-exposure.

Early in its use, carbon disulphide was found to cause symptoms of acute mania, hallucinations, and dementia in workers exposed to high concentrations. Some of these effects were permanent and associated with changes in the cerebral cortex and ganglion cells. Carbon disulphide was first reported to cause peripheral neuritis in 1904. In 1950 pre-senile arteriosclerotic changes were noted in workers exposed to carbon disulphide. These changes occurred in workers aged 42 to 55. There was evidence of cerebral, renal and myocardial sclerosis.

In its early use under conditions of inadequate control, exposure to TEL resulted in acute mania ('looney gas').

Mercury vapour and mercury compounds are also known to produce emotional symptoms. The term 'mad as a hatter' is related to the central nervous system effects of mercury. The word 'erethism' is commonly used in toxicology textbooks describing the adverse effects of mercury on behaviour.

Acute exposures to methyl bromide have been associated with the development of permanent neurotic and psychotic conditions.

In recent years much attention has been given to behavioral studies of workers exposed to chemical agents, particularly to solvents. Most of these reports have come from Scandinavian sources and they are briefly reviewed below.

In 1976 Axelson, et al., reported a case control study of neurophychiatric disorders among workers exposed to solvents. They found early retirement due to mental disorders was more common among controls. No differences in mental function existed between painters and controls at the age of military service.

Hanninen, et al., reported in 1976 on the behavioural effects of long term exposure to a mixture of organic solvents. Winneki and Focks reported that paint strippers using methylene chloride at concentrations of about 500 ppm showed decrements in manual dexterity and attention lapses.

In 1978 Seppalainen described neurophysiological effects of long term exposure to a mixture of organic solvents. Knave, et al., in the same year presented data from their study of 30 workers exposed to jet fuel and a matched control group of 30. The jet fuel workers were exposed for an average of 17 years to a concentration of about 300 mg/m^3. Exposed workers and controls were subjected to special examination and tests directed to behavioral and central nervous system effects. The examining team included an occupational physician, psychiatrist, psychologist, neurophysiologist, and others. The authors noted significant differences in the incidence and prevalence of psychiatric symptoms, loss of attention, reduced sensorimotor speed, etc.. The author attributed these differences as probably due to exposure to jet fuel.

In 1979 Barrowcliff and Knell reported the case of a 60 year old male worker exposed for 20 years to between 500 and 1,000 ppm of methylene chloride. He developed a dementia which the author attributed to endogenous carbon monoxide brought about through the metabolism of methylene chloride.

Elofson, et al., described their cross-sectional study of 80 auto and industrial spray painters with long-term exposure to organic solvents. The painters were compared to 2 matched control groups of workers not exposed to solvents. The investigation included psychiatric interview, psychometric, neurological, neurophysiological, and ophthalmological examinations. A computer tomography study of the brain was included. The authors concluded that the psychiatric tests indicated a slight cerebral lesion. The psychometric tests showed significant differences between the solvent workers and controls in respect to reaction time, manual dexterity, perceptual speed and short term memory. No difference was found with respect to performance on verbal, spatial or reasoning tests. Significant differences were found in peripheral nerve function. The worker exposed to solvents had a higher vibration threshold. Differences were also noted on the ophthalmological and computer tomography examinations. The authors noted that these changes occurred at airborne levels which were less than the permissible exposure levels in Sweden.

Engholm and Englund in 1982 compared the mortality of 30,580 construction painters with 18,521 plumbers and both were compared to the national mortality in Sweden. The construction painters showed an excess mortality for many causes of death including psychosis, neurosis and alcoholism. Suicide in painters was twice that of plumbers but similar to the national average. The authors concluded that exposure to solvents caused a typical alcohol-related disease panorama.

Lauwerys, et al., in 1983 published details of their study of 22 subjects exposed to perchloroethylene in 6 dry cleaning shops in Belgium. The exposed workers were compared to a match group of 33 control subjects. The solvent exposure for the exposed group averaged 21 ppm The authors concluded that exposure to perchloroethylene for 6 years at concentrations below the permissible exposure level of 50 ppm produced no adverse effect on the central nervous system.

Waldron in a paper intended for presentation at this session of MEDICHEM submitted details of his study of various groups of workers as follows:

27 exposed to styrene in making boats
30 exposed to styrene in making bus panels
56 exposed to methylene chloride
15 exposed to paint solvents, (toluene, xylene, and 1,1,1-trichloroethane)
99 controls not exposed to solvents

A battery of tests similar to those employed in Sweden was used. Waldron concluded that few effects were observed "that can unequivocally be attributed to long-term exposure to solvents".

Nephrotoxicity

The kidney is rich in blood supply (over 100 times that of resting muscle). It consumes a large amount of oxygen and is involved in many active transport phenomena involving glucose, amino acids, etc. The kidney is divided into 2 parts which have different functions.

1. Cortex. The cortex is involved in gluconeogenesis, fatty acid use, prostaglandin catabolism, cytochrome P450 reactions, drug metabolism, Vitamin D metabolism, deamination, etc.

2. Medulla. The predominant function of the medulla is glycolysis. It is involved in lipogenesis and prostaglandin synthesis.

The kidney plays an important role in detoxification, excretion and re-absorption. These activities make the kidney a sensitive target organ for toxic substances.

The mechanism by which toxic action is produced in the kidney are summarized as:

1. Effects on renal blood flow which decreases the glomerular filtration rate (GRF) e.g. analgesics.

2. Toxic effects on tubule cells e.g., cadmium, carbon tetrachloride. The proximal tubules are most affected.

3. Immunologically mediated effects.

4. Obstruction of tubules or ureter e.g. oxalic acid.

5. Neoplasia

Nephrotoxic effects from metals and metallic compounds

Nordberg noted that about 20 metals or their compounds are capable of causing renal effects. In regard to metals 2 special factors are of importance:

1. Absorption. Only about 10% of ingested insoluble metal salts are absorbed; 90 to 100% of soluble metal salts are absorbed. Absorption or ingestion varies with the type of compound. For example about 10% of ingested inorganic mercury is absorbed whereas about 100% of ingested methyl mercury is absorbed.

2. Binding of metals in blood plasma. Binding of metals is essential for transport, biotransformation, and renal uptake. Various mechanisms of binding metals are possible. Some examples are noted:

   - Beryellium - as colloidal phosphate absorbed to plasma alpha globulin.
   - Uranium - partly complexed with bicarbonate in plasma and partly bound to plasma protein.
   - Cadmium - protein bound in plasma

Metals which bind to low moleculer weight protein (M.W. < 30,000) may permit excretion, re-absorption and accumulation of metals in the renal tubule. Ceruloplasmin and transferrin carry out transport functions for copper and iron respectively.

Metallothionein (MW about 6500), rich in sulphhydryl groups may bind with several metals including cadmium, mercury, copper, zinc, silver, bismuth, and gold. Metallothionein occurs mainly as intracellular protein. If released to the plasma, it may be taken up in renal tissue as a result of glomerular filtration and tubular re-absorption. Metallothionein is normally found as foetal and neo-foetal protein. It is formed as needed to regulate zinc and copper plasma levels. Certain non-essential divalent metal ions can cause induction of metallothionein. Divalent nickel, lead, silver, beryllium, etc. may induce metallothionein directly or they may induce its formation indirectly by increasing the liver content of zinc the renal concentration of copper.

Cadmium

The kidney is the target organ for cadmium. Cadmium causes tubular damage resulting in proteinuria, aminoaciduria, glycosuria and phosphaturia. Swedish researchers have developed modeling studies which show that the critical renal cortical level of cadmium is 200 micrograms per gram of renal cortex. This concentration would be produced by an airborne concentration of 40 $\mu g/m^3$ inhaled over 25 years of occupational exposure.

The role of exposures to cadmium as a cause of hypertension is controversial. Bosquet in 1977 claimed that low environmental exposures to cadmium may be an important cause or hypertension. There is no evidence for this claim.

Mercury

Mercury vapour and mercury compounds cause diffuse damage to the proximal tubule. Mercurial nephrosis has been well documented in the liver. In order of nephrotoxicity, mercury vapour and its compounds are numbered in this descending order: mercury vapour, divalent mercury compounds, phenyl mercury, ethyl mercury and methyl mercury.

Lead

Lead is nephrotoxic producing damage to the proximal tubule. This is seen in severe acute poisoning in children and in heavy occupational exposure to workers.

Very high doses of lead given orally over the lifetime of the rat produce adenoma and adenocarcinoma of the kidney tubules. This is not found in hamsters or rabbits. Lead compounds have not been found to be mutagenic. Epidemiological studies of workers exposed to lead have not shown any evidence of increased risk of kidney cancer.

In another experiment, lead acetates administered with a known carcinogen (N - (4 - fluorobiphenyl) 4 - acetamide) increased the tumor yield to 100%. This has raised questions about the role of lead compounds as promoting agents.

Severe acute poisoning with lead has been linked to subsequent hypertension but this is not true for occupations with low lead level exposures. Beevers et al. felt there was a connection between lead and hypertension as they found increased lead plasma levels in hypertensive patients. Nephropathy has not been associated with occupational exposure to lead.

Gold

Gold salts used in the treatment of rheumatoid arthritis (aurothioglucose and gold sodium aurothiomalate) cause nephrotoxicity in some patients.

Platinum

Divalent chloroplatinates have been found to be potent asthmagenic agents on inhalation. Nephrotoxicity has not been associated with occupational exposure. Cisplatin (cis - dichlorodiamine Platinum II), an anti-tumor drug used in the treatment of testicular and ovarian cancer, has been found to be nephrotoxic in some treated patients. Cisplatin affects the proximal tubules.

Uranium

Soluble uranium compounds are nephrotoxic. Uranyl nitrate causes acute renal failure through glomerular damage and reduction in the glomerular filtration rate.

Chromium

Bichromates in very high doses may cause tubular renal damage. Nephrotoxicity in workers exposed to chromium and chromium compounds is not common.

Lithium

Chronic oral administration is suspected of being capable of causing renal interstitial damage. This has not been a problem in occupational exposure.

Vanadium

O-vanadate exposure has been reported to cause kidney damage. O-vanadate inhibits Na-K-ATP activity in the tubule. Occupational exposure to vanadium compounds has not been associated with nephrotoxicity.

Nephrotoxic effects from organic compounds

Several halogenated hydrocarbons are known to cause damage to the renal tubules. There is adequate scientific documentation of this. There have been reports of nephrotoxicity from petroleum distillates and other solvents but generally these involve high acute exposure.

Carbon tetrachloride

Carbon tetrachloride causes damage to both liver and kidney. When taken orally, the liver damage predominates. When inhaled, the kidney damage predominates. There are many case reports of death from acute tubular damage from exposure to carbon tetrachloride. The toxic effects of carbon tetrachloride on both liver and kidney, but primarily the liver, are enhanced on Monday morning exposure following heavy alcoholic intake on the preceding weekend.

A number of volatile chlorinated hydrocarbons including carbon tetrachloride, chloroform, and trichloroethylene may be associated with sudden death due to fatal cardiac arrhythymia in which the endogenous release of epinephrine is implicated.

Chloroform

Nephrotoxic effects have been reported but are rare.

Trichloroethylene

Kidney lesions following inhalation have not been reported. Near lethal amounts of trichloroethylene, when injected intraperitonealy into experimental animals, produced only transient renal damage.

Perchloroethylene

This solvent is widely used in dry cleaning. Although occasional reports of renal damage have been reported, this has not been a significant occupational health problem.

Dibromochloropropane (DBCP)

This substance was used as a soil fumigant and pesticide. Experimental studies in rats showed it capable of causing kidney and testicular damage. Sterility was produced in male workers exposed to DBCP in its manufacture. No renal damage was reported.

Ethylene dibromide

This substance is used as a fumigant and as a scavenging agent in leaded gasoline. Ethylene dibromide was found to cause kidney damage and produce cancer in experimental animals.

Hexachloro-1,3-butadiene

Hexachloro-1,3-butadiene is a chemical intermediate. Inhalation in rodents resulted in kidney damage. Chronic oral feeding studies showed renal epithelial hyperplasia and adenocarcinoma in both male and female rats.

Vinylidene chloride

Inhalation of 25 ppm by mice for 1 year leads to the development of adenocarcinoma of the kidney.

Dichloroacetylene

Dichloroacetylene is a by-product of the synthesis of certain chlorinated aliphatic hydrocarbons, e.g. in the synthesis of vinylidene chloride. Dichloroacetylene is a highly nephrotoxic compound. Reichert et al. exposed mice and rats to dichloroacetylene by inhalation. Mice and rats both died of acute nephropathy showing extensive tubular necrosis. Animals which survived 18 months of exposure showed cystic degeneration of tubules and increase in cystic adenoma in both male and female mice and in male rats.

The results observed with dichloroacetylene are similar to those of hexachlorobutadiene, one of the main degradation products of dichloroacetylene.

S-(1,2-dichlorovinyl) -L-cysteine (DCVC)

DCVC causes acute renal necrosis in animals tested. DCVC is not active but is converted to an active metabolite which produces the kidney damage. DCVC was identified in cattle feed (soya bean meal) which has been extracted with trichloroethylene. Cattle consuming the treated soya bean meal developed aplastic anemia. DCVC was synthesized and fed to rats. In rats it caused acute renal tubular disease; rats metabolized DCVC differently than cattle.

Ethylene glycol

Ethylene glycol is used primarily as an auto antifreeze and solvent. When ingested, kidney damage is produced by deposition of analate crystals in the kidney tubules. Inhalation exposure in the workplace has not produced renal damage.

Diethylene glycol

This solvent produced kidney damage when ingested in a pharmaceutical preparation. Inhalation exposure in the workplace has not led to kidney damage.

Other solvents and mixed solvents

Askergran in 1982 studied three groups of workers exposed to solvents and one control group. The groups were made up as follows:

52 exposed to styrene in boat manufacture
42 exposed to toluene in photoengraving work
40 exposed to paint solvents containing toluene, xylene and other solvents
48 controls - not exposed to solvents

The author sampled urine from all groups for cells, proteins, creatinine, glucose, osmolality, and renal clearance using 51 chromium - EDTA complex. Askergran noted that renal damage in humans from solvent exposure is associated with "massive exposure". There is no proof of kidney damage from slight to moderate exposure. Some increase in albumin content and in cellular content was found but no impairment of GFR. The author considers that kidney damage from solvent exposure at the workplace is an open question.

Franchi et al., studied 438 workers exposed to four groups of solvents as follows: mixed aliphatic and alicyclic solvents in the C_5 to C_7 range, styrene, a mixture of toluene and xylenes and to a mixture of chlorinated hydrocarbons. Exposure levels were measured. Renal function tests included total proteinuria, albuminuria, and urinary excretion of muramidan. The author found little evidence of renal damage due to the solvent exposure. Total proteinuria was increased in workers exposed to styrene and albumin. The damage was mild and reversible.

The study of Lauwerys et al. on twenty-two subjects exposed to perchlorothylene was referred to earlier. These authors found no evidence of kidney damage when levels were maintained below the recommended limits.

Gasoline

Dr. L. Goldberg has already presented a summary of the findings of this study. Rats were exposed to gasoline over three years at airborne concentrations of 67,292 and 2056 ppm. Male rats developed renal tumors. Dr. Goldberg noted that the yield of these tumors was low, they did not metastasize, they were not considered as lethal neoplasms, and they were related to unique metabolic transformation in the rat kidney.

Occupational cancer

Earlier speakers have referred to some of the occupational cancer hazards in the petrochemical and chemical industry. These include: skin cancer from contact with heavy, high boiling lube oil fractions containing polynuclear aromatic hydrocarbons, leukemia from exposure to benzene, and liver angiosarcoma from exposure to vinyl chloride. Dr. R.E. Eckhardt has also discussed the studies on brain cancer among workers in the chemical industry. Skin cancer in mule spinners exposed to Scottish shale oil has been widely documented.

Dr. R. Morgan described the results of his prospective chart study of petroleum refinery workers. He found no significant excess of any cancers although there was a statistically insignificant excess of leukemia deaths noted. Whether this is related to benzene exposure cannot be determined until further information is available on employment groups.

Blot et al., compared mortality in 39 counties where petroleum refinery was done and 117 counties with petroleum refining. The petroleum refinery workers lived in the 39 counties where they worked. The author matched the 2 groups for geographic region, population size, age, sex, and other demographic indices. They found a significant excess of cancer of the stomach and rectum for males in the petroleum counties. The author also noted an excess in the petroleum countries for lung cancer, nasal cancer, skin cancer and sinus cancer among the males.

Wigle carried out a similar study in 2 Canadian cities in 1977. He compared the mortality rates in Sarnia (where 28% of the male labour force worked in petroleum refining and/or chemical industry) with that of London (where none of the workers were so employed). Wigle found no significant difference in cancer mortality between the two centers.

Theriault and Goulet reported on their historical chart epidemiological study in 1977 among Montreal refinery workers. They found an excess of brain cancer.

A number of historical chart empidemiological studies have demonstrated increased risk of cancer. Harris et al. found an excess of deaths from cancer of the esophagus, stomach and lung among Canadian workers exposed to crude petroleum. Refinery workers also showed an increase of intestinal cancer when compared to non-refinery workers.

Thomas et al. carried out a proportional mortality study of union members from 3 Texas refineries. They found an excess of stomach cancer, leukemia, multiple myeloma, lymphomas and brain tumors among petroleum refinery workers.

Rushton and Alderson carried out a historical prospective study of U.K. refinery workers and compared their mortality to the mortality rates of England and Wales and of Scotland. Lung cancer mortality was much less than expected. Cancer of the esophagus, stomach, intestines and rectum was increased among workers in some refineries.

A mortality study of Swedish construction painters by Engholm and Englund has been referred to earlier. A chart of 30,580 painters was followed from 1966 to 1974. The mortality pattern in this chart was "similar to that seen in alcoholics". Increased risk of cancer of the esophagus, lung and intrahepatic ducts was observed.

In recent years experimental toxicology and epidemiological studies have been carried out with 1,3-butadiene - a major petrochemical product used in the making of synthetic rubbers and copolymers. In 1977 a long term inhalation study in rats showed increases in the incidence of tumours of the zymbal gland, thyroid, mammary glands, uterine sarcoma and pancreatic adenoma. In 1982 another experimental inhalation study was terminated because of the high incidence of malignant lymphoma and other tumours which occurred. In 1982 an epidemiology study involving 13,920 workers followed from 1943 to 1979 showed increased risk of several cancer types. Maintenance workers showed increased risk of several cancer types. Maintenance workers showed increased risk of cancer of the testis, larynx, esophagus, stomach, large intestines and Hodgkin's disease. In three other occupational groups. The incidence of Hodgkin's tumour was increased. Because of these data, the Threshold Limit Value Committee of the American Conference of Governmental Industrial Hygienists has proposed listing of 1,3-butadiene as a carcinogen without an assigned TLV.

Reproductive hazards

Tests for teratogenicity in animals exposed to high and low doses of Stoddart solvent, toluene, mixed xylenes, unleaded gasoline, high aromatic solvent, n-hexane, diesel fuel, VM & P naphtha, kerosene, rubber solvent, jet fuel A., and Number 2 heating oil were all negative. Benzene exposures at 40 ppm (120 mg/m^3) induced a statistically significant increase in partial resorption in rats.

Holmberg carried out a case control study in which he compared birth defects among infants born to mothers exposed to organic solvents during their pregnancy. Holmberg found an excess of central nervous defects. This work was followed up over the following 3 years. Hrupa et al. found no association between work with solvents and central nervous system defects.

The episode involving sterility in males exposed to 1,2 dibromo - 3-chloropropane (DBCP) has been widely publicized. DBCP was produced from petrochemical feedstock. In 1977, concern was raised about infertility in male workers engaged in the production of DBCP. 142 workers were examined with the following results noted:

Group	Number	Azoospermia Percent	Oligospermia Percent
Exposed to DBCP	107	13.1	16.8
Never Exposed	35	2.9	0

Testicular biopsy was carried out in the most severe cases and showed the absence of all spermatogenic activity. There was a good correlation between years of exposure and spermatocyte depression.

Alcohol intolerance

The health effects of concern to the occupational health professional range from acute toxicity, subchronic toxicity, chronic toxicity, behavioural effects, allergic effects, fibrogenic effects, mutagenicity, teratogenicity, carcinogenicity, etc. To these effects we might also consider those exposures which may evoke unusual toxic responses (exposures which interfere with alcohol intake after leaving the job, etc.).

Chemicals which contain the carbon-sulphur group may be metabolized in the body producing metabolites which cause alcohol intolerance. This is manifested by flushing, headache, nausea after consumption of beer, wine or spirits. Chemicals which are associated with this effect include:

Disulphuram	- rubber accelerator
Thiuram	- fungicide
Carbon disulphide	- solvent, xanthating agent
N-Butraldoxine	- antioxidant
Calcium cyanamide	- fertilizer

Summary and conclusions

This review has ranged over a number of current occupational health problems which may affect workers in all industry sectors. In many ways, the chemical industry is at the leading edge in the development, production and use of new chemical products for the betterment of people. Because of this, the chemical industry has a responsibility to conduct pre-marketing testing, health surveillance of its workers, provision of material safety data sheets, adequate labelling of its products, education of its workers, research into long-term health effects of exposure to chemical agents, and provision of early warning of newly discovered or suspected health effects from exposure to chemical agents. In Canada, the chemical industry has maintained a high standard in the prevention of occupational accidents and diseases among its workers.

Neurotoxic effects may be produced by a large number of metals, inorganic metal compounds and organometallic compounds. The major effect is peripheral neuropathy. Methyl mercury is widely appreciated as an important neurotoxic agent; it is particularly of concern because of its ability to damage the developing foetal and neonatal brain. The neurotoxic effects produced by metals are from relatively high exposure levels. - well above the recommended exposure levels used by most national authorities. There is no evidence to support the view that "heavy metals" in the levels encountered in the workplace or in the general environment are a cause of such neurological diseases as amyotrophic lateral sclerosis, Guillian-Barré syndrome, neuromuscular disorders, Altzheimer's disease, etc. Exposure to lead in the general atmosphere in cities has been cited as the cause of behaviour and learning disabilities in young children. Evidence of this is not at all clear. Recent large scale studies conducted in the U.K. have concluded that there is no demonstrable effect with current airborne environmental levels. The major concern for urban children in slum areas is from ingestion of old lead paint, a major problem in some U.S. cities.

A number of organic chemicals are well known as the cause of peripheral neuropathy n-hexane, methyl n-butyl ketone, acrylamide monomer and carbon disulphide. The exposure levels necessary to produce peripheral neuropathy with those agents is well above permissable exposure levels established by various national authorities and generally involve gross skin exposure. There is no evidence that other commonly used organic solvents in use including Stoddart solvent, toluene, mixed cyclenes, high aromatic solvent, diesel fuel, kerosene, VM & P naphtha, rubber solvent, jet fuel A., heating oils, trichloroethylene, perchloroethylene, 1,1,1-trichloroethane, alcohols, glycols, ketones and styrene, cause peripheral neuritis or other neurological diseases when used in keeping with normal hygienic practices.

The role of exposure to common industrial solvents, paint solvents, hydrocarbon fuels, and solvents used in plastics fabrication in the causation of central nervous system disease and behavioural changes has been raised. Many of these reports have come from Swedish studies in which the exposure level to the solvents is said to be below the current Swedish exposure limits. Others have not been able to demonstrate differences in neurological function and behaviour between solvent-exposed workers and controls. Waldron applied some of the same battery of tests used to study British workers exposed to solvents. While he found some differences, he could not relate these unequivocally to solvent exposure. While the Swedish studies appear to be well done, a large number of dependent and independent variables are involved. It would appear useful to design a sufficiently large group for study of this important question. In general, some of the published studies on this subject refer to the solvent exposure in general terms. Environmental data are lacking or sparse. The possibility of single high acute exposures does not appear to have been addressed. The possible effect of other exposures does not seem to be taken into account, e.g., curing agents, hardeners, plasticizers, pigments, colourants, inhibitors, stabilizers, metal dusts, etc. I would prefer to see better characterization of the total exposure before I would accept that the solvent exposures described produce such important neurological and behavioural effects.

In regard to nephrotoxicity, it is important to note the role of the kidney in metabolism, excretion and re-absorption. Protein binding of metals is important for some of their agents. Since re-absorption of low molecular weight proteins occurs, deposition of metals in the renal tubules occurs as with cadmium. The kidney is the critical target organ for Cadmium and Swedish researchers have estimated the critical burden for the renal cortax as 200 ug/g renal cortex. I would not expect any risk of renal toxicity from the inorganic metal dusts if exposure levels are maintained below the currently applicable exposure limits. Many halogenated hydrocarbons typified by carbon tetrachloride are capable of causing renal tubule damage in high exposure. The control of airborne exposure levels and the precautions about skin contact generally provide an adequate margin of safety to prevent nephrotoxic effects. In my review I have noted a number of recent studies in which workers exposed to solvent showed no impairment of renal function.

There are significant anatomic and metabolic differences between the kidney of rodents and man. It would appear that some metabolites produced in the rat kidney are unique to that species. Because of this, care and prudence is needed in extrapolating these rodent studies to man. This criticism is similar to that made in experiments involving liver cancer in mice exposed to chlorinated hydrocarbons.

Exposure to polyaromatic hydrocarbons in high boiling lube fractions may present a risk of skin cancer in machine operators if inadequate controls and personal hygiene are not observed. Benzene is known as the cause of leukemia in workers. The epidemiological studies done on petroleum refinery workers do not seem to present a clear or consistent picture. The studies lack clear description of occupational groups and environmental exposure data. Several of the studies, however, point to the possible increase in mortality from cancer of the digestive tract. I believe that further epidemiological studies are needed on petroleum refinery workers.

The vinyl chloride story must serve as an object lesson to the chemical industry. Occupational health professionals in the chemical industry should maintain continued vigilance by observing the disease and mortality pattern of chemical workers. I agree with the advice given by Professor Doctor A.M. Thiess in his opening remarks. Good employment, exposure and health records should be maintained by the chemical industry.

In regard to reproductive hazards, it does not appear that the commonly employed solvents present any documented reproductive hazards apart form exposure to DBCP which, hopefully, represents an isolated episode.

Health surveillance, environmental monitoring, good record systems will continue to occupy the attention of dedicated health professionals. This MEDICHEM Conference offers an excellent opportunity to exchange the latest information, and to build and renew contacts with colleagues in the occupational health field.

OCCUPATIONAL EXPOSURE TO CADMIUM AND THE EXCRETION OF β_2 - MICROGLOBULIN

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Abstract

Eighty-eight workers exposed to cadmium were surveyed between 1979 and 1982.

Determinations were made of cadmium in blood and urine, and of protein excretion. The low molecular weight protein β_2-microglobulin was employed as a specific indicator for renal tubular dysfunction.

The cadmium concentration in blood was closely correlated with that in urine and with the β_2-mircroglobulin excretion, independant of the workers' ages. β_2-microglobulin excretion decreased and rose parallel with the cadmium concentration in the blood..These results indicate that at least minor tubular dysfunction is reversible.

Résumé

Quatre-vingt-huit travailleurs exposés au cadmium ont fait l'objet d'analyses de 1979 à 1982.

L'étude comprend les dosages du cadmium dans le sang et l'urine et l'analyse de l'excrétion de protéine. Le faible poids moléculaire de la protéine β_2-microglobuline a été employé comme indicateur spécifique de l'anomalie tubulaire rénale.

Car la durée de l'exposition professionnelle et la concentration sanguine de cadmium ont un rapport statistique significatif à la concentration β_2-microglobuline qui suit de près les changements de concentration sanguine du cadmium.

Ces résultats indiquent que l'anomalie tubulaire mineure tout au moins est réversible.

Summary

The following findings were obtained on examining 88 workers exposed to cadmium in a factory for cadmium pigments and stabilizers.

1. There is a comparatively close correlation between the cadmium concentration in the blood and that in the urine.

2. The cadmium concentration in the blood is most closely correlated, independently of age, with the β_2-microglobulin elimination.

3. Over the period in which the study was made, viz. 1979-1982, the β_2-microglobulin excretion does not remain the same, as would be expected theoretically, but runs parallel with the cadmium concentration in the blood. This suggests that the disturbance in microglobulin absorption in the proximal tubule is reversible, at least in the range of comparatively low internal cadmium concentrations. Presumable morphological changes are still not involved at this stage but only reversible enzyme inhibition.

Thus β_2-microglobulin elimination can be taken as a parameter for occupational exposure to cadmium.

Introduction

The kidneys are regarded as the critical organs affected by long-term exposure to cadmium. It is assumed that, after glomerular filtration, the cadmium-metallothioneine complex is reabsorbed in the proximal parts of the tubuli contorti and deposited there.

It appears that the tubules are predominantly affected, and perhaps the glomeruli as well, by kidney injuries induced by cadmium. The occurrence of tubular injury has been scientifically verified on a wide basis. It has not been definitely proved that glomerular injury, at least in the early stages, is caused by cadmium in human beings.

The pathophysiology of cadmium injury to kidneys has not yet been completely clarified. An early symptom is increased excretion of proteins with a low molecular weight, and this can be regarded as evidence of a reabsorption disturbance in the tubuli contorti. Since the tubulus region of the kidneys, particularly the proximal tubule, is that with the highest energy requirements, it is here where toxic effects first become evident.

β_2-Microglobulin with a molecular weight of 11,800 dalton is taken as a measure for proteinuria if the proteins are of low molecular weight (Kjellström & Piscator, 1977; Schaller et al., 1978; Zainuddin et al., 1981).

In contrast to β_2-microglobulin, creatinine and urea are removed by dialysis and do not yield any direct information on the possibility of tubular injury. Consequently, toxic disturbances of the kidneys through the tubules can be recognized earlier by a change in the β_2-microglobulin concentration in the urine than by other routine laboratory methods.

Aim

In 1977, it was pointed out, mainly by Kjellström and Piscator, that β_2-microglobulin excretion could not, strictly speaking, be taken as a parameter for biological monitoring of workers exposed to cadmium, because increased excretion is already a sign of irreversible tubular injury.

Since this question has still remained open, we decided to investigate it. We studied the relationship between the parameters for the internal cadmium concentration (cadmium in the blood and urine and duration of exposure) and the β_2-microglobulin excretion, which was taken as the exposure level parameter. The necessary data were obtained from biological monitoring, in which 88 workers exposed to cadmium were examined in the period from 1979 to 1982.

The β_2-microglobulin was determined by radio-immunoassay by the Pharmacia, Uppsala method (Zainuddin, 1981). Cadmium was determined by atomic absorption spectroscopy.

Results

Forty-eight of the 88 workers were engaged in the production of cadmium pigments; and the other 40, in the production of stabilizers containing cadmium.

The following values were obtained for the exposure level, i.e. the concentration in the place of work, for workers who were obliged to wear masks and were not employed in zones of particularly high concentration.

TABLE 1: Cadmium Concentration Measured in μg/m^3 of Air

Betrieb Plant	1979	1980	1981	1982
Cadmium Pigments	97	49	50	26
Cd Stabilizers	–	29	55	30

The only difference in the Student t-test between the two groups was the average duration of exposure. There were no differences in age, the cadmium concentrations in the blood and urine, and the β_2-microglobulin excretion.

As a result, the two groups were taken together for further evaluation.

TABLE 2: Correlation Cadmium Pigment and Cadmium Stabilizer Workers

Production		Age (years)	Expos. period (years) (µg/dl)	Cm blood (µg/dl)	Cm urine (µg/l)	β_2-Microglob in urine
Cadmium Pigment	n	48	48	48	48	48
	x	42.1	8.4	0.93	9.60	102
	s	10.3	5.5	0.52	7.82	155
		n.s.	t = 2,594**	n.s.	n.s.	n.s.
Cadmium Stabilizers	n	40	40	40	40	40
	x	39.57	5.1	1.00	8.10	106
	s	11.2	3.9	0.56	7.56	154

t**: $p < 0.01$

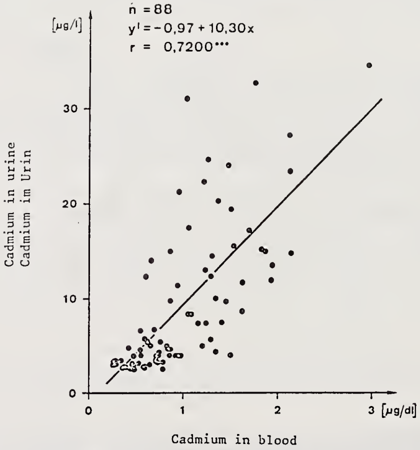

Figure 1: Correlation Cadmium/Urine and Cadmium/Blood

There was a close correlation between the cadmium concentration in the blood of the 88 persons examined and the amount of cadmium eliminated in urine.

B₂-microglobulin and cadmium/urine

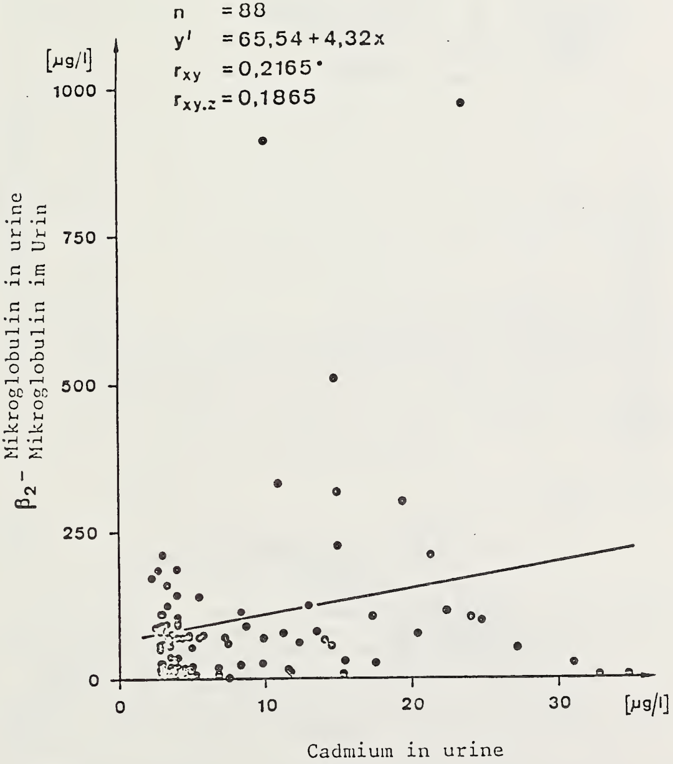

Figure 2: Correlation Cadmium/Urine and ß₂-Microglobulin/Urine

The relationship between the cadmium concentration in the urine and the amount of ß₂-microglobulin excreted is shown in Figure 2. If the age is kept constant by calculating the partial correlation coefficients, the relationship is not significant.

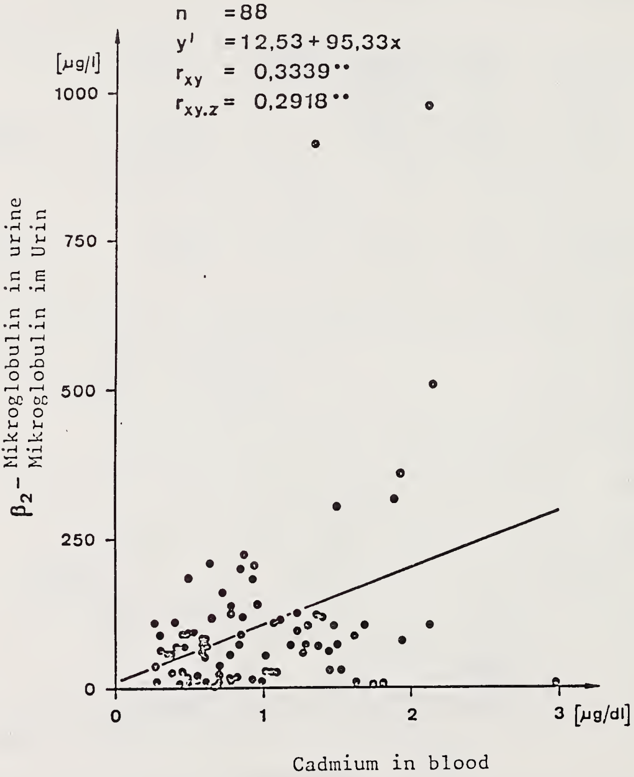

Figure 3: Correlation Cadmium/Blood and ß₂-Microglobulin/Urine

B_2-Microglobulin and Duration of Exposure

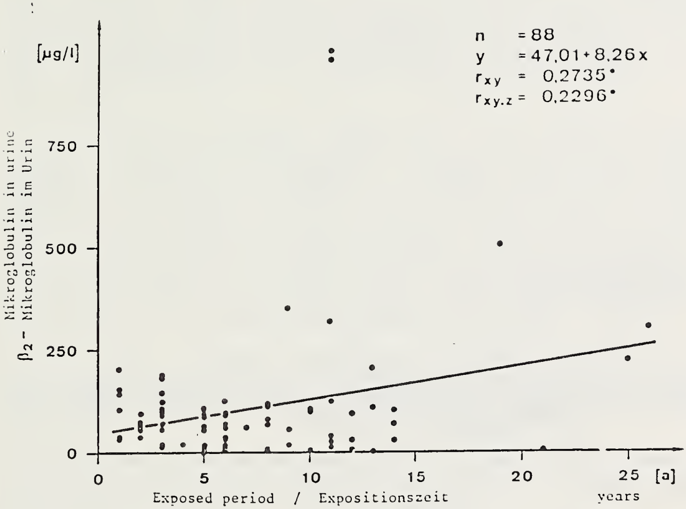

Figure 4: Correlation Exposed Period (Years) and β_2-Microglobulin/Urine

The cadmium concentration in the blood is statistically correlated with the amount of β_2-microglobulin eliminated in the urine.

If the duration of exposure is taken as a measure of the exposure level, a significant correlation with the β_2-microglobulin eliminated in urine can be again determined. Once again, if the age is a constant, the correlation remains significant with a partial correlation coefficient of 0.2296.

TABLE 3: Blood and Urine Camium Concentration Rearranged According to Current BAT Values

		Blood (µg/dl)		Urine (µg/dl)	
		0-1.49	1.50	0 - 1.49	1.50
Cadmium	n	73	15	71	17
	x	0.77	1.88	5.75	22.16
	s	0.36	0.37	3.44	6.31
ß₂-Microglobulin in Urine 320 µg/l	n	1	3	3	1

TABLE 4: Characteristics of Four Workers with ß₂-Microglobulin in Urine Exceeding 320 µg/l

	1	2	3	4
Age (years)	38	55	51	61
Exposed period (years)	11	19	9	11
Cadmium in blood (µg/dl)	2.12	2.14	1.93	1.34
Cadmium in urine (µg/l)	23.5	14.8	11.0	10.0
Creatinine in serum	0.87	0.83	0.98	0.87
ß₂-Microglobulin in Urine (µg/l)	977	511	359	913

The data on the internal cadmium concentration and the elimination of β_2-microglobulin have been rearranged in Table 3 according to the current biological tolerances (BAT values) for cadmium issued by the Senatskomission zur Prüfung gesundheitsschädlicher Arbeitsstoffe. In 73 of the 88 persons examined, the blood cadmium concentration was less than 1.5 µg/dl; the mean value in this case was 0.77± 0.36 µg/dl. In 15 of those examined, the cadmium blood concentration of 1.5 µg/dl was exceeded; in this case, the mean figure was 1.88 ± 0.37 µg/dl.

The amount of cadmium eliminated in the urine of 71 of those examined lay below the BAT value of 15 µg/l; in this case, the mean value and standard deviation were 5.75 ± 3.44 µg/l. The cadmium excretion for 17 of those examined was higher than 15 µg/l; in this case the mean value was 22.16 µg/l and the standard deviation was 6.31 µg/l. Four workers had a β_2-microglobulin excretion higher than 320 µg/l(Table 4). In three of them, the BAT value for cadmium was exceeded, either in the blood or in the urine. The following figures for these four persons are listed in the lower part of the table; age, duration of exposure, cadmium in blood and urine, creatinine in serum, and β_2-microglobulin excretion.

A slight tubular proteinuria has been detected in individuals Nos. 1, 2 and 4 by further diagnostic techniques, viz. phenylacrylamide gel electrophoresis, nephrography and blood urea clearance. Thus a slight tubular kidney injury is indicated.

A point of clinical importance is that none of these individuals suffered kidney injury of pathological significance.

Cadmium/blood and β_2-microglobulin 1979-1982

The clinical history of 44 of the 88 individuals examined could be followed for a fairly long period, viz. from 1979 to 1982.

The graphs for the measured cadmium concentrations in the blood and the β_2-microglobulin excretion in the urine for these individuals are reproduced in Figure 5.

The concentration of cadmium in urine for these workers is not shown here but remains practically constant over the period of time concerned. We consider that it is worth noting that the β_2-microglobulin excretion rises and falls in parallel with the cadmium concentration in the blood.

Discussion

We consider that of the findings mentioned the following three are important.

1. The cadmium concentration in the blood is closely correlated with that in the urine.

2. The cadmium concentration in the blood is most closely correlated with the β_2-microglobulin excretion and is independent of the workers' ages.

3. Over the period of time in which the study was made, the β_2-microglobulin excretion does not remain constant, as would be theoretically expected, but decreases in parallel with the cadmium concentration in the blood and rises with it again in 1982.

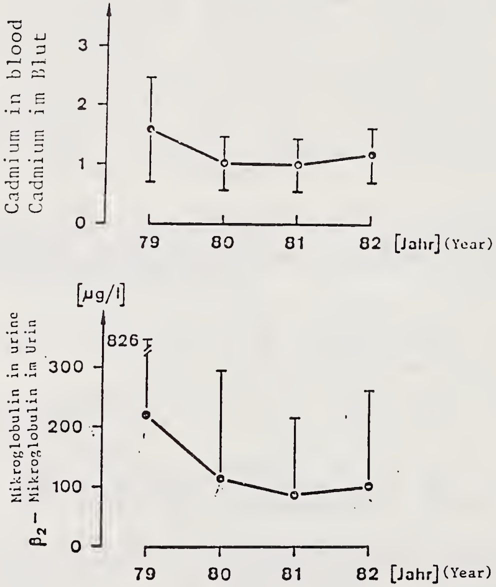

Figure 5: Correlation Cadmium/Blood and Years 1979 - 1982 and Correlation β_2-Microglobulin/Urine and Years 1979 - 1982

There is a close linear correlation between the cadmium concentration in the blood and that in the urine. This can be explained by the fact that the workers were examined over a number of years and by 1982 the external exposure level was comparatively uniform. Thus the cadmium in the blood was in equilibrium with that stored in various other parts of the body. This explanation agrees well with findings made by Lauwerys et al. in 1976 and 1979 on the kinetics of cadmium absorption.

It has been shown that a decrease in the actual inner cadmium concentration, as measured by the blood cadmium level, is accompanied by a parallel decrease in the $ß_2$-microglobulin excretion. In the light of this fact, we consider that the disturbance in microprotein absorption in the proximal tubule is reversible, at least in the range of comparatively low cadmium concentrations. It can be presumed that this stage in reabsorption disturbance can be ascribed to reversible enzyme inhibition and not to morphological changes.

Hence, despite the opinion expressed by Kjellström and Piscator (1977), the $ß_2$-microglobulin excretion can be taken as a parameter in determining occupational exposure to cadmium.

This interpretation has been confirmed by experiments carried out on rats by Gonich and Raghavan (1983). These authors found that the glycosuria and aminoaciduria dropped slowly 4-5 days after parenteral cadmium administration had ceased.

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RESPIRATORY EFFECTS OF FORMALDEHYDE IN THE SHEEPSKIN PROCESSING INDUSTRY

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Abstract

This pilot survey was an investigation into the effect of formaldehyde on the respiratory function of employees engaged in fur and sheepskin processing. Assessment of acute effects on the large and small airways, current respiratory status and the prevalence of respiratory disease was carried out. As accurate an assessment as possible was made of employee formaldehyde exposure. Two groups of workers were studied. One group was exposed to fur, sheepskin and formaldehyde and a second group to fur and sheepskin only. Controls were taken and matched for age and smoking. Lung function tests included forced expiratory volume in one second, forced vital capacity and maximum expiratory flow volumes. Individuals exposed to formaldehyde showed a significant fall (p 0.001) across the shift both at the beginning and end of a working week. Of interest was that the mean fall in FEV_1 was greatest in the sections where heat was applied to the skins. There was no evidence of acclimatisation. There was no evidence of diminishing lung function over the working week. This was true even when those employees who had been exposed to formaldehyde for more than ten years were considered separately. A similar fall in flow volumes occurred in individuals exposed to formaldehyde. There was good correlation between formaldehyde in air levels and fall in FEV_1 across the shift. The current respiratory status of employees exposed to formaldehyde was also considered. This group of workers showed a significantly lower FEV_1 when compared with the mean predicted volume; however, the mean forced vital capacity was not significantly different from the predicted. The effect of formaldehyde appeared to be both on the large and small airways and was reversible. The response to formaldehyde appeared to be that of a direct irritant. In this study, there was no evidence that exposure to fur and sheepskin impaired respiratory function.

Résumé

Cette étude pilote constituait une analyse des effets de la formaldéhyde sur la fonction respiratoire des employés du domaine de la transformation des fourrures et des peaux de mouton. L'évaluation des effets aigus sur les grandes voies

respiratoires et les petites, de l'état actuel de la respiration et de la fréquence des maladies respiratoires a été effectuée. Une évaluation aussi précise que possible de l'exposition des employés à la formaldéhyde a également été réalisée. Deux groupes de travailleurs ont été étudiés. Un groupe a été exposé à la fourrure, la peau de mouton et la formaldéhyde, tandis qu'un second groupe etait exposé à la fourrure et à la peau de mouton seulement. Des groupes témoins ont été utilisés et appareillés selon l'âge et l'habitude de fumer. Les épreuves de fonction pulmonaire comprenaient le volume expiratoire forcé (VEMS) en une seconde, la capacité vitale forcée et les volumes de débit expiratoire maximum. Les personnes exposées à la formaldéhyde ont présenté une baisse importante (p 0.001) au cours du quart, à la fois au début et à la fin de la semaine de travail. Il est à remarquer que la baisse moyenne du VEMS était plus prononcée dans les secteurs où la chaleur était appliquée aux peaux. Il n'y a eu aucune indication d'acclimatation et aucune indication du'une réduction de la fonction pulmonaire au cours de la semaine de travail. Il en était ainsi même lors de l'examen individuel d'employés, exposés à la formaldéhyde pendant plus de dix ans. Une baisse semblable dans les volumes de débit s'est produite chez les personnes exposées a la formaldéhyde. Il y avait une bonne corrélation entre la formaldéhyde dans l'air et la baisse du VEMS au cours du quart. La situation respiratoire actuelle chez les employés exposés à la formaldéhyde a également été examinée. Ce groupe de travailleurs présenté un VEMS appréciablement inférieur lorsque'il était comparé au volume moyen prévu. Cependant, la capacité vitale forcée moyenne n'était pas différente de façon significative de la valeur prévue. L'effet de la formaldéhyde semblait être celle d'un irritant direct. Au cours de l'étude, il n'y a eu aucune indication que l'exposition à la fourrure et à la peau de mouton nuisait à la fonction respiratoire.

Introduction

There is a wealth of literature on the biological effects due to exposure to formalin solution and formaldehyde gas in both humans and animals. There is however, a paucity of work on the assessment of acute and chronic effects on the respiratory tracts of employees with unmixed exposure to formaldehyde. Such studies which are reported do not include detailed formaldehyde in air measurements. In the fur and sheepskin processing industry this question is of importance, as formaldehyde is essential in the dressing of fur skins and indeed all patents for "topping solutions" for the "pointing" of sheepskin wool contain formalin for which there is no known substitute. The action of formaldehyde here is that by entering into chemical union with the extended fibre it permanently sets it. This particular factory had existed since 1940 and had a fairly stable workforce. A pilot study was carried out on site in an attempt to answer the question - did "formaldehyde" at air levels existing in the factory cause respiratory tract damage?

Fur itself may be allergenic and possibly cause respiratory damage (Pimental, J.C., 1970). The study was designed to exclude any effects for which fur or wool alone could be held culpable (i.e. the respiratory status of employees exposed to fur and sheepskin only was also investigated).

The aims of the study were:

1. Assessment of acute effects on large airways. For this, simple spirometry was used to measure FEV_1 and FVC before and after work and at the beginning and end of a work week.

2. Assessment of current respiratory status of the work groups by comparing the FEV_1 and FVC with their predicted values and with control populations.

3. The earliest adverse effects of occupational and environmental factors on the lung are probably changes in the small airways (<2mm in diameter). Maximum expiratory flow volume curves were used to assess this and to serve as a baseline for ongoing study of these groups.

4. As accurate an assessment as possible was made of formaldehyde exposure of employees engaged in the various stages of fur and sheepskin processing.

5. The prevalence of respiratory symptoms and disease was assessed within groups and their control populations.

No attempt was made to study the "sensitising" action of formalin and formaldehyde.

Formaldehyde is a colourless gas with a pungent odour, which is readily detected below levels of 1 ppm of the gas in air.

Aqueous solutions of formaldehyde in water contain 30 - 50% of dissolved formaldehyde by weight. Commercial preparations of formaldehyde are available in grades of methanol-free or methanol-stabilised (10 - 15% of methyl alcohol added as a polymerisation inhibitor or reagent). Formaldehyde polymerises readily in both the liquid and the solid state. In the vapour phase formaldehyde exists as a monomer, whereas its chemistry in aqueous solutions is more complex. Reactions of formaldehyde with itself depend primarily upon temperature and concentration and stability of the monomer depends on its purity.

Biological effects

Formaldehyde is a highly irritant gas and a protoplasmic poison. The general toxicity of aldehydes appears to decrease with increasing molecular weight. This is probably related to the primary irritant action of the lower molecular weight substances. The primary irritant action of formaldehyde is probably due to the reactivity of formaldehyde with proteins and amino groups, imidazole and thiols (Catch 1974, Janvillier et al. 1959, Martin 1975). Formaldehyde reacts with terminal hydrogen atoms, particularly in the free amino groups of amino acids. Cyclic compounds and cross linking of protein chains by way of methylene bridges may occur.

The main toxic effects of formaldehyde are:

1. Primary irritation of the skin, eyes and mucosa of the respiratory tract.

2. Contact dermatitis of the skin from primary irritation.

3. Sensitisation of the skin and respiratory tract.

Many other effects have been recorded but the above are the most adequately documented and substantiated.

Chronic effects

Formaldehyde is ciliatoxic and is a component of cigarette smoke. Studies are conflicting. Some consider the physiological action of formaldehyde to be limited entirely to the upper respiratory tract as the amount of the irritant gas which actually reaches the lungs depends to a large extent on the solubility of the gas. Formaldehyde is highly soluble in water and therefore a considerable amount is removed through the respiratory tract. However, with regard to functional lung changes, formaldehyde cannot be dismissed as merely an upper respiratory irritant as some workers considered the toxicity of formaldehyde was enhanced by the presence of inert aerosols.

Absorption

In 1972 Egle, using tracheotomised mongrel dogs showed the total tract retention of formaldehyde was nearly 100% regardless of the ventilatory rate, formaldehyde concentration or tidal volumes measured; for the range of concentrations studied both the upper and lower parts of the respiratory tract were shown to be effective absorbers of formaldehyde. Amdur 1959, 1960, showed the greatest changes were observed in tracheotomised animals receiving both formaldehyde and NaCl aerosol. All responses within an exposure group were proportional to the concentration of formaldehyde however.

The sheepskin industry

Since 1930 the processing of wool sheepskin has developed to such an extent as to constitute virtually a separate industry. This followed the discovery of the effect on sheepskin produced by treatment with formaldehyde followed by heating. This effect made it possible to produce a shorn sheepskin with a high gloss which did not revert to kinkiness or curl in contact with moisture, a defect which had limited all previous attempts to use sheepskin in the fur trade.

Formaldehyde is then, essential for the "pointing" of the wool and there is no substitute as a dressing. The chemistry of formaldehyde treatment on wool is complex but it probably destroys or it blocks the hydrophilic groups which give rise to the effect of kinkiness or curl when wet and they must be altered by the effect of formaldehyde. They are chemically imino and amino groups.

The dressing and dyeing of sheepskin involves specialised techniques due partly to the nature of the raw material and partly to the necessity of the treatment of the wool. Sheepskin possesses a heavy comparatively thick pelt with sharply defined grain and flesh layers. The fur trade demands a light weight supple leather for its garments. The dressing must be able to withstand the heat of the rotary irons. Apart from the application of formaldehyde, the preparation for dyeing is mechanical.

Three machines play the major role in this preparation - ironing, shearing and carding machines.

The number of heated rotary irons determines the output since ironing is the critical stage in the preparation of sheepskin. Shearing machines reduce the length of the wool. Carding remove tangles and felting. the processes consist of a series of card, iron and shear treatments until the wool is uniform and level. Formalin is then applied by "topping", that is a hand brush treatment. This is followed by a series of 3-4 "passes" on the rotary irons until the wool is considered sufficiently "cooked", that is weather proofed or set. Ironing temperatures are in the range of 180° to 220° above which the wool will start to discolour.

Subjects, materials and methods

This factory employed 208 people in all. The dressing and finishing area were in a separate building from that in which the skins are received, the fur storage area. These two buildings had separate entrances. Dyeing was carried out in yet another building. There was little job rotation within this factory. A five day week was worked Monday to Friday.

The processes carried out in the dressing and finishing area were topping, glossing, white ironing, staking, shearing, carding and sorting (i.e. quality control). Each ironing machine and the topping bench had exhaust ventilation. Each man was responsible for collecting his own "topped" skins from the central storage area which he stacked near his machine for ironing. Exhaust ventilation was installed in this factory about 10 years ago and at no time had respiratory protection been worn. The total number of employees in the main dressing shop was 30.

Two groups of workers were included in this study. These groups were entirely separate during the work day.

Group I

This group consisted of employees exposed to fur, sheepskin and formaldehyde. These individuals worked in the main dressing and finishing shops.

Group II

This group consisted of employees exposed to fur and sheepskin only. That is, they worked in the storage area where the skins were handled on arrival at the factory.

Control population to Groups I and II

These were taken from a stores and warehouse department at a large neighbouring factory. They were not exposed to any respiratory irritants as far as is known. This was not an "end" occupation in this factory. These men lived in the same area as the above groups and there was no evidence to indicate any social class differences.

Controls were individually matched to Groups I and II for age and smoking habits. It was, however, impractical to attain matching for height.

Population	Work Area	Number
Group I	Main dressing and finishing shop (Exposure to Sheepskin, Formaldehyde)	30
Group II	Storage area (Exposure fur, sheepskin)	15
Control Population (to Groups I & II)	Stores and warehouse (neighbouring plant)	45
Leavers during past 5 years (Group I & II Area)	Past exposure as in Group I, II areas	11

Procedure

There was not a medical officer at the firm and pre-placement health screening was not carried out. These men could be regarded as a survivor population. All employees who had left the firm during the last 5 years and had worked in

Group I and II areas were identified and contacted. This did not prove difficult as all still lived in the locality. All consented to interview and application of the Respiratory Questionnaire and all leavers also agreed to lung function testing.

All individuals studied were male Caucasians. The groups included smokers and non-smokers. There were no ex-smokers.

Details of name, address, date of birth and occupational histories were recorded. The Medical Research Council Respiratory questionnaire 1966 was completed by the same interviewer for each individual. A full smoking history was recorded and a history of atopy for future use was also included.

Measurements

Standing height in stocking soles was measured to the nearest half centimetre.

Ventilatory functions tests

These were carried out by the same examiner and using the same instrument throughout in a standardised fashion using the McDermott spirometer. Readings of 5 blows were taken and the mean of the last 3 blows corrected to BTPS recorded. Pre- and postshift testing was performed on Monday and Friday.

In Groups I and II reading commenced at 5:45 a.m. and 2:45 p.m. Individuals were tested at the same time on Friday as on Monday, both pre- and postshift, so that changes across the shift on the two days could be compared, that is diurnal variation was accounted for. (McDermott, M. et al. 1966, Guberan and Walford et al. 1969).

Unfortunately because of the work system controls could not be tested post shift until 4:00 p.m.

All readings were carried out within 1 month to eliminate any seasonal variation.

Predicted values of FEV_1 and FVC were calculated using the regression coefficients for height and age of Kory et al. 1961, 1963.

Maximum respiratory flow volume curves

The same McDermott spirometer as above was used and the mean of three blows after two practice blows was taken and corrected to BTPS.

During the forced expiration an additional output was obtained from the digital electronics and recorded on a monotape cassette recorder which was battery operated. The output consisted of a train of 0.2 ms pulses at 2 ms intervals, negative pulses representing the increment of volume every 10 ms as a four-bit number and a positive pulse signifying the beginning of a number. The four-bit number (1,2,4,8) gives the volume increment in 10 ml steps up to 150 ml in 10 ms, which is equivalent to a flow rate of 15 litres/sec. If a volume increment was < 10 ml, then it was included in the next 10 ms sample. The signals were independent of tape speed and stretch and could be fed via an integrated store of 1024 bits directly into a Hewlett-Packard programmable calculator (Type 9830) for the calculation of flow and volume. The integrated circuit store could be incorporated with the spirometer electronics. The calculator had outputs to a page printer and x-y plotter.

Derivation of volume and flow from tape

Volume and flow were obtained using finite difference methods (NPL 1957). The volume ^{v}n was the sum of the increments of volume Δn.

$$Vn = {}^{n}\sum \Delta^{n}$$

The flow^{v} n was calculated from the volume increments using the central difference formula.

$$Vn = 1/2m \sum_{n-m+1}^{n+m} \Delta n$$

Only the volume calibration of the spirometer and the use of a stable oscillator were required for obtaining flow.

Predicted values were calculated using the formula of Schilling and Bouhuys.

Environmental measurements

Only Draeger tube measurements were available up to the time of this survey. These readings had been fairly constant in the various sections over the past 5 years as measured by this method.

Ten years ago exhaust ventilation was installed. Levels pre- and post-exhaust ventilation had been recorded.

Present survey

Static and personal sampling

Formaldehyde could be determined with considerable sensitivity by the purple colour formed with chromotropic acid, (Altshuller, A.P. et al. 1961).

The investigator was advised that this was the most useful test with regard to sensitivity and overall utility. Formaldehyde in air could be determined in a concentration range of 0.01 to at least 200 ppm by this method. It was a simple and rapid procedure, and as interferences are minor, this method has been adapted for air pollution work and for these reasons the chromotropic acid method was chosen, for both static and personal sampling.

Static sampling

Ten sampling points were selected, two points in each of the five work sections in Area I. Identical sampling points were used on the four days of sampling. Static sampling was also carried out at 2 points in the Group II area. The factory was an old building and had no cavity wall insulation.

Personal sampling

Two employees in each of the sections wore the sampling tubes on their left lapel and care was taken to place the tubes in identical positions on each of the four days of sampling: two of these days being those on which lung function testing was carried out. The sampling tubes consisted of aluminium tubes of internal diameter 16 mm and length 150 mm containing silica gel activated by drying at 110°C. The dust sampler was a portable Retheroe Mitchell type L2C.

Results

In the study the level of significance was taken as 5% and where Student's t-tests were used all were 2-tailed.

TABLE I: Group Characteristics

Group	Number	Number of Smokers	Mean Age	Mean Height cm
Group I	30	22	40.4	172
Group II	15	10	44	176
Control Gr I	30	22	40.7	176
Control Gr II	15	10	44.3	177

Leavers over the last 5 years from areas I and II

These numbered 11 in all, 8 employees from Area I and 3 from Area II. All agreed to interview, the application of the respiratory questionnaire and lung function tests. Two men from Group I area had retired at 65 years having been employed from 18 and 21 years at the factory. One man from Group II area had died. No person had left either because of respiratory symptoms or respiratory disease. All those under 65 years were actively employed in fairly heavy physical work. Most had left for increased remuneration. One man had died at the age of 56 years of coronary heart disease.

Spirometry results

Paired comparisons for the FEV_1 and FVC were made across the shift on Monday and Friday testing for Groups I and II and on Monday for the two groups of controls.

Group I

On Monday testing there was a mean fall in FEV_1 of 0.314 litres and a mean fall in FVC of 0.108 litres across the shift. On Friday there was a mean fall of 0.321 litres in FEV_1 and 0.082 litres in FVC.

The falls across shift on Friday were compared with Monday.

There was no significant difference between the Friday and Monday falls in FEV_1 and FVC.

Preshift FEV_1 and FVC levels on Friday were compared with Monday levels. There was no significant difference.

Group II

Monday testing showed a higher postshift mean FEV_1 of 3.83 litres when compared with a preshift mean of 3.69 litres. The postshift FVC was also higher on postshift testing, 4.78 litres as compared with 4.73 litres. On Friday similar results were obtained. On paired comparison of pre- and postshift readings, the rise in FEV_1 across the shift on Monday and Friday was significant ($p<0.001$). The rise in FVC was not significant on Monday but was on Friday.

The change on Friday testing was compared with Monday and was not significantly different on the two days.

Neither the FEV_1 nor FVC differed significantly when Friday and Monday readings were compared.

Controls

The mean FEV_1 and FVC readings for controls to Groups I and II were slightly lower postshift. On paired t-testing the difference across the shift was not significant.

These results indicated that some agent present in the environment of Group I was causing airway obstruction as all employees in this group had a fall in FEV_1 and FVC on both Monday and Friday.

The rise in FEV_1 and FVC due to circadian rhythm described by Guberan and Walford occurred in Group II workers but as the controls were tested 1 1/2 hours later than Group I and II this rise was not evident.

The environment of Group I differed only in the presence of "formaldehyde".

These results did not indicate deterioration over the work week.

Group II

Neither the FEV_1 nor FVC differed significantly when Friday and Monday preshift readings were compared.

In an attempt to confirm that an environmental agent was causing the fall in FEV_1 in Group I employees a random sample of five men from Group I were tested across the shift after putting them to work in the fur storage area for the whole shift - it was found that in no individual was there a fall of FEV_1 or FVC.

It was therefore considered that "formaldehyde" was the possible causative agent of the airways obstruction in Group I employees.

Smoking

Cigarette and cigar smoke contains formaldehyde. A 14 ml puff of cigarette smoke contains 4.1 micrograms of formaldehyde (Egle, J.L. 1972).

Group I

Comparisons of change across the shift in smokers and non-smokers on Monday and Friday were made using the unpaired t-test. Individuals had not smoked 1 hour prior to lung function testing.

On Monday the mean fall of FEV_1 in smokers was 0.32 litres as compared with a mean fall of 0.302 litres in non-smokers. The mean fall in FVC was also greatest in smokers. On Friday also, the falls were greater in smokers than in non-smokers. The differences, however, were not significant.

Adaptation

This has been reported to occur with regard to the lachrymatory and odour effects produced by formaldehyde, but is quickly lost once exposure ceases. It would have been interesting to see whether adaptation occurred with respect to the large airways obstructions, if indeed formaldehyde was the causative agent.

Unfortunately serial readings across the shift whereby rates of fall could be assessed would have proved disruptive to the system of work. However, comparisons were made of the fall in FEV_1 on Monday and Friday in those employees with greater than and less than 5 years service.

This was repeated using 10 years employment. There was no suggestion of an adaptive mechanism. In fact the mean fall of FEV_1 across the shift was significantly more on both Monday ($p<0.02$) and Friday ($p<0.05$) in employees with greater than 5 years service. Using greater than 10 years again the fall across the shift was greater in those with more than 10 years service but this was not significant at the 5% level.

Comparison of "hot" and "cold" sections

Glossing and white ironing involves the ironing of the formalin "topped" skins. The ironing temperature was 180-220°C. The falls in FEV_1 and FVC were compared using the unpaired t-test in employees in the "hot" and "cold" sections. On both days of testing the fall in FEV_1 was greater in men in the "hot" section as compared with the "cold" section employees. The difference was significant at the 5% level. The mean fall in FVC on both days although slightly greater in men in the "hot" as compared with the "cold" sections was not significantly different.

Although falls in FEV_1 occurred in men in the cold sections it is possible that the effect of heat on the skins produced some unknown general air-borne contaminant in this building. To ascertain whether this could be possible, Management consented to two irons being placed in the Group II (storage) area and non-"topped" skins were ironed.

The Group II men ironing non-"topped" skins during a shift did not experience a similar fall in FEV_1.

Flow volumes at 50% and 25% of vital capacity

The aim of using maximum flow curves was:

1. to detect early changes in small airways narrowing and
2. to provide a baseline for follow up studies.

Predicted values were calculated using the formula of Schilling and Bouhuys.

Group I

On Monday the mean flow at 50% of vital capacity was 5.15 litres/sec preshift as compared with 3.74 litres postshift.

Paired comparisons of pre and post shift levels showed a significant fall across the shift ($p<0.001$). There was also a significant fall across the shift on Friday testing ($p<0.001$).

The mean flow volume at 25% although slightly lower postshift than preshift was not significant at the 5% level, on both Monday and Friday testing.

The falls across shift Monday and Friday were compared and were not significantly different at 50% or 25% of vital capacity.

Comparison of Monday and Friday preshift levels gave higher mean readings on Friday than on Monday, this was not significant in flow at 50% of vital capacity or at 25% of vital capacity. Therefore there was no deterioration in flow volumes across the work week.

Group II

The preshift mean flow volume at 50% of vital capacity was 4.35 litres/sec as compared with a postshift mean of 4.39 litres/sec. The difference however, was not significant at the 5% level, neither was the mean rise postshift in flow volume at 25% of vital capacity. Similar findings occurred on Friday. Again the changes across shift were not significantly different on Monday and Friday. Nor did deterioration in flow volume curves occur across the working week.

Smoking

Group I

The mean change in flow at 50% of vital capacity was a fall of 1.45 litres/sec. in non-smokers and a fall of 1.4 litres/sec. in smokers. The mean fall at 25% of vital capacity was 0.22 litres/sec. in non-smokers and 0.05 litres/sec. in smokers. The difference in falls across shift between smokers and non-smokers was not significant.

Adaptation

The change in flow over the shift was compared in those employed less than and more than 10 years. The mean fall in flow at 50% of vital capacity was 1.611 litres/sec. in those with less than 10 years service as compared with a mean fall of 1.018 litres/sec. in those with greater than 10 years service. The difference was not significant at the 5% level. The changes across the shift were not significantly different for flow at 25% of vital capacity when long and short term workers were compared.

Group II

Both with flow at 50% and 25% of vital capacity the rise was greater in those with more than 10 years service and at 25% those with less than 10 year exposure showed a mean fall of 0.003 litres/sec.

The differences of change over the shift were not, however, significant.

Hot and cold sections

The fall across shift in flow volume at 50% of vital capacity was greater in the hot section than the cold on both Monday and Friday testing. The difference in the falls between the hot and cold sections however was not statistically significant. Conversely the falls in flow at 25% of vital capacity was slightly greater in the cold section on both days, although the difference was not statistically different.

Formaldehyde in air levels

Present survey

Static samples using the chromotropic acid technique on 10 samples 4 days of testing gave a mean level of formaldehyde in air of 2.17 ppm. Personal samples gave a mean of 2.2 ppm formaldehyde in air.

The highest formaldehyde in air levels were in the topping and sorting sections.

Fur storage area

Formaldehyde in air was not detected in this area using the sampling method mentioned above.

Formaldehyde in air levels and fall in FEV_1 across the shift

Personal sampling results and the individual's fall in FEV_1 across the shift on Monday and Friday were used. Linear regresssion analysis was performed using all results. The regression line y = a + bx was fitted by the least square method. (Figure 1).

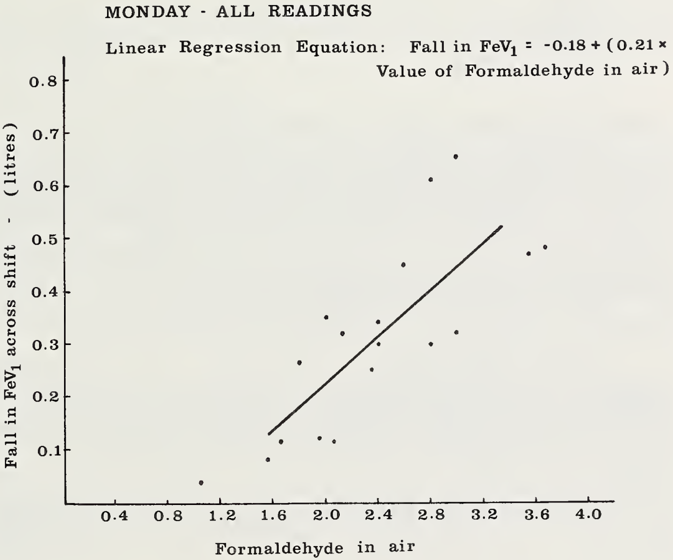

Figure 1: Formaldehyde in Air Levels and Fall in Forced Expiratory Volume Across the Shift

Formaldehyde in Air Levels (Personal Sampling) and Fall in FEV_1 across the Shift

Monday	Correlation Coefficient
All Results	$r = 0.82$
"Hot" Sections	$r = 0.95$
"Cold" Sections	$r = 0.93$
Friday	
All Results	$r = 0.64$
"Hot" Sections	$r = 0.99$
"Cold" Sections	$r = 0.80$

Comparison of Group I and II with their controls

As the subjects were closely matched for relevant factors, such as age and smoking (height being cancelled in $FEV_1/FVC\%$), the paired comparison test for a difference between means would be a more sensitive test than that for two independent samples. However the increase in precision depends on the correlation being positive and high. The correlations between Group I and controls and Group II and controls were positive but low and therefore the unpaired t-test was using to compare $FEV_1/FVC\%$ in Groups I and II and their respective controls.

Assessment of respiratory state by duration of employment

As exhaust ventilation was installed in the Group I area ten years ago, those employed for more than 10 years had been exposed to high formaldehyde in air levels as recorded by Draeger tube measurements. Employees with greater than 10 years service were compared with those with shorter service.

Group I

The mean FEV_1 as a percentage of its predicted value was 88% in the longer term employees as compared with 97% in workers with less than 10 years service. The difference was significant ($p<0.05$).

The FVC expressed as a percentage of the predicted value, although less in employees with more than 10 years service was not significantly different, neither was the $FEV_1/FVC\%$ after adjusting to the mean age of Groups I and II, that is: 42 years.

The flow volumes at 50% and 25% of vital capacity expressed as a percentage of the predicted value was higher in those with less than 10 years service, the difference, however, was not significant. Similar findings occurred in the flow volume at 25% of vital capacity.

Group II

In this group also the mean FEV_1 and FVC expressed as a percentage of their predicted values were lower in those who had worked at the factory for more than 10 years ago as was the $FEV_1/FVC\%$ after age adjustment to the mean age of the groups. The differences were not, however, significant.

The mean flow volumes although lower at 50% and 25% of vital capacity in the long term workers when compared with employees with less than 10 years service were not significantly different.

Current respiratory status

Although the investigation concerned formaldehyde, these workers were also exposed to fur and sheepskin. Any respiratory effects in Group I may then have been due either to the "formaldehyde", the fur, or both. Therefore Group II was taken to look at the effect of fur and sheepskin only and controls to both groups selected to compare respiratory status.

Controls to Group I

The mean FEV_1 preshift level was 3.24 litres/sec as compared with a mean predicted value of 3.66 litres/sec. The difference was significant ($p<0.01$).

Group I

Here the mean FEV_1 was slightly lower than predicted mean 3.47 litres/sec as compared to 3.66 litres/sec. The difference was significant ($p<0.01$). The FVC was not significantly different although lower than the predicted values. The mean flow at 50% of vital capacity was 5.15 litres/sec as compared with a predicted mean of 4.27 litres/sec. The difference was significant ($p<0.01$). At 25% flow, again the mean of this group was higher than the predicted mean, but the difference was not significant.

Group II

Both the mean FEV_1 and FVC were higher in this Group than their predicted means. The difference was not significant for FEV_1, but was for FVC ($p<0.02$). The mean flow at 50% of vital capacity was 4.35 litres/sec as compared with a predicted mean of 4.26 litres/sec and the mean flow at 25% was also higher in the Group than that predicted. These differences were not significant at the 5% level.

Leavers

The predicted values for FEV_1 and FVC in leavers from

Group I and II did not differ significantly from their predicted mean values. There was no significant difference in the $FEV_1/FVC\%$ when Group I was compared with Group I leavers or when Group II leavers and Group II were compared, the $FEV_1/FVC\%$ having been age adjusted to the mean age of Groups I, II and the leavers (44 years).

As it was felt that the regression equation of Kory et al. might not "fit" the individuals in this study, it was decided to repeat the analysis of FEV_1 and compare the mean values after adjusting for age and height using the regression equation calculated from the data. Differences between the adjusted means were tested for significance using an analysis of covariance.

There was no statistically significant difference between the regression planes and the means were therefore adjusted using the common regression coefficients based on the pooled data. The overall difference between the adjusted mean was statistically significant ($p<0.001$), therefore the "t" distribution was used to compare pairs of adjusted means.

The observed mean FEV_1 of Group I did not differ significantly when compared with the adjusted mean derived from within the Group regression and the observed mean FEV_1 was somewhat higher than the adjusted mean. The difference between the mean FEV_1 and predicted mean was less when compared with the adjusted mean.

Respiratory symptoms

Respiratory symptoms were those derived from the Medical Research Council Questionnaire. Groups I, II and their Controls were compared using the Chi square test. There was no significant difference at the 5% level. (X^2 = 3.045 2.df).

Respiratory disease

This was derived from the Medical Research Council Questionnaire. Groups I, II and their Controls were compared using the Chi square test. There was no significant difference. X^2 = 1.216 p 0.01.

Discussion

The aim of this pilot survey was to determine whether any acute and/or chronic effects on the large and small airways of the lung could be attributed to formaldehyde exposure. Simultaneously as accurate an estimate as possible of individual exposure, during a working day, to formaldehyde was obtained. Fur may cause asthma (of an immunological type) and possibly allergic alveolitis (Pimental, J.C. 1970). Therefore, a group of men exposed to fur and sheepskin only was studied and controls were selected. Measurement techniques were standardized and bias was accounted for as far as possible. This population could be regarded as a survivor group, therefore, employees who had left the firm within the last 5 years were also included.

This survey showed both large and small airways obstruction across the shift in all Group I employees. Airway obstruction did not occur in Group II employees or the controls.

The only treatment of the skins in the Group I area was the application of formalin. The effect of heat on the skin alone did not reproduce these falls in FEV_1, FVC and flow volumes. It was therefore concluded that "formaldehyde" was the causative agent although the larger drop in FEV_1 and FVC across the shift in employees in the hot section sight indicate an additive effect of polymerisation products of formaldehyde. These would not have been detected as the chromotropic acid method measures formaldehyde as the volatile monomer and not its polymers, some of which are known respiratory irritants. This was of interest as past work on formaldehyde exposure has been somewhat conflicting. Schoenberg. J.B. et al. 1975, investigated exposure to phenolic resins. They found low FEV_1/FVC% and MEF_{50}/FVC% ratios in those exposed to the resin fumes for more than 5 years when they compared them with non-exposed smokers. These effects were reversible. They also stated the extent of chronic airways obstruction. However, they found only small decreases in pulmonary function during the work-day and work-week and only Draeger tube measurements of formaldehyde were quoted. This was a mixed exposure as employees were also exposed to phenolic fumes. Gamble, J.F. et al. 1976, studied rubber workers exposed to a phenol-formaldehyde type resin. They found significant reductions across the shift in expiratory flow rates at low lung volumes in workers exposed to hexamethylenetetramine resorcinol, these effects were reversible. They found no association between changes in peak flow and environmental levels of resorcinol, formaldehyde, hydrogen, cyanide or ammonia. Here again, a group exposed to a mixture of pollutants was being followed. They also found an excess of respiratory symptoms in this group.

In the present study there was no evidence of the adaptation described by various authors regarding upper respiratory tract symptoms when the large and small airways effect discussed here were considered. Neither was there evidence of an increased effect due to the presence of the formaldehyde in cigarette smoke. In the present study there was good correlation between formaldehyde in air and fall in FEV_1 across the shift. The airways obstruction would appear to be reversible as there was no deterioration in lung function over a five day work-week.

Formaldehyde is highly soluble in water (100% absorption in the upper respiratory tract is quoted by Egle, 1972). In this study, effects on the small airways were also noted. This may have been due to absorption of formaldehyde onto particulates or aerosols, as was described by Amdur in animal experimentation using sodium chloride aerosols. The site at which aerosol particles come into contact with a responding tissue is an important determinant of the nature and severity of resulting effects. Alternatively, a less soluble polymer of formaldehyde might be incriminated as the causative agent in the small airways effect.

The greater fall in lung function tests noted in the longer term workers may be attributable to increased sensitivity of the "irritant" receptors in the airways. Sensory nerves in the airways may be exposed by damage to the bronchial epithelium caused by toxic gases or chemicals resulting in a lowering of the threshold for activation of the sensory nerve endings (Nadel, J.A. 1976, Gold, W.M. 1973). There was no evidence in this study of acute effects caused by fur or wool, in spite of the dusty operations involved.

Chronic

Formaldehyde is ciliatoxic and lowers ciliary activity (Dalham, T. et al. 1956). Also formaldehyde can alter tissue properties as described by Sugihara, T. et al. 1975. This occurs by the forming of intermolecular cross-linkages in the protein of the alveolar tissue which reduces the maximum extensibility of alveolar wall. This is found in normal ageing and with the irreversible obstructive pulmonary syndrome.

Although the mean FEV_1 of Group I employees was significantly lower than that predicted (using the regressions on age and height of Kory et al.) the observed mean FEV_1 value did not differ markedly when compared with the adjusted mean derived from within the group regression. Of interest was that the controls had lower FEV_1 and FVC's than their predicted means. Again, the difference between the controls' mean FEV_1 and predicted mean was less when compared with the adjusted mean. It might have proved of value to use the regressions for age and height derived within the study group rather than that of the population used by Kory et al.. However this population was small (90). In this study, fur and sheepskin exposure did not produce chronic lung effects. There was no evidence of an increased prevalence of respiratory symptoms or disease when Groups I and II employees and their controls were compared by the Chi square test. It was interesting to note that flow volume results in all groups, when compared with their predicted values (using the formula of Schilling and Bouhuys) showed higher mean values. This might have been due to the different instrumentation used in their study or to differences in the populations studied.

Conclusions

In this group of individuals exposed to formaldehyde there was evidence of a repeated irritant insult to the large and small airways. Gross chronic effects were not apparent, neither was there an increased incidence of respiratory symptoms or disease.

Inferences are not drawn regarding the fur and sheepskin industry in general and these results are applicable only to this particular population.

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STUDIES ON THE STRUCTURE-TOXICITY RELATIONSHIP OF INDUSTRIAL CHEMICALS

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Abstract

In chemical industries, it has become more important to know and predict the toxicological properties of chemicals of the present and future. We studied the relation between physicochemical structure and toxicity.in acrylamide derivatives, acrylate compounds and organic nitriles.

For acrylamide and its derivatives, a linear discriminant analysis between neurotoxic and non-neurotoxic derivatives showed that P, the partition coefficient between n-octanol and water, and q_2, the charge density of C-2 carbon, are important to determine their neurotoxicities. For acrylates and methacrylates, the acute toxicity was found, by multiple regression analysis, to be significantly dependent upon P and log k, the second order rate constant with reduced glutathione, especially upon P, being the correlation coefficients -0.9909 for acrylates and -0.759 for methacrylates. Some organic nitriles produce acute toxicity by liberating cyanide ions in the body. After analysing the relation between structure and the acute toxicity, we found that they seemed to be divided into two groups with regard to the relation of P and the toxicity, one having a parabolic and the other a linear function. These findings may provide basic information for a better understanding of the toxic properties of these chemicals.

Résumé

Dans les industries chimiques, il est devenu important de connaître et de prévoir les propriétés toxicologiques des produits chimiques actuels et futurs, et les études portant sur les relations entre la structure physico-chimique et la toxicité semblent constituer une démarche prometteuse à cet égard. Le présent document expose certains des résultats de nos études pertinentes sur les dérivés de l'acrylamide, les composés acrylates et les nitriles organiques.

Pour l'acrylamide et ses dérivés, une analyse discéminante linéaire entre les dérivés neurotoxiques et non-neurotoxiques a montré que P, le coefficient de séparation entre n-octanol et l'eau, et q_2, la densité de charge de carbone C-2, sont importantes pour déterminer leurs neurotoxicitées. Pour les acrylates et les méthacrylates, la toxicité aigüe a été reconnue, par analyse de régression multiple, comme dépendant de façon significative de P et log k, le taux de second ordre constant avec une réduction de glutathione, spécialement avec P, étant les coefficients de corélation -0.9909 pour les acrylates et -0.759 pour les méthacrylates. Certains nitriles organiques produisent une toxicité aigüe en libérant des ions de cyanure dans le corps. Après avoir analysé le rapport entre la structure et la toxicité aigue, ils semblent être divisés en deux groupes en ce qui a trait au rapport de P et de la toxicité, l'un ayant une fonction parabolique et l'autre une fonction linéaire respectivement. Ces résultats pourraient constituer des données de base pour une meilleure compréhension des propriétés toxiques de ces produits chimiques.

Introduction

With the increasing number of chemicals in industries and in our daily life, it has been of great importance to evaluate their biological effects properly. Although it is our final aim to know the effect of each compound precisely, we are confronted with many difficulties because of the vast numbers of chemicals we have to study.

Under such conditions, the study of structure-activity relationships, one of the theoretical approaches to toxicology, seems to be a way of challenging these difficulties. We should like to introduce some of our recent studies in this field.

The studies

The first example of our studies is the discriminant function analysis of the neurotoxicity of acrylamide and its analogues. It is well-known that chronic exposure to acrylamide monomer causes neuropathy to human beings as well as experimental animals. We have already shown that some of its analogues also cause similar symptoms but some others do not (1,2). We usually test the neurotoxicity of chemicals by using the rotarod method and histopathological observations.

It seems very interesting and important to know the reason for dividing the analogues into neurotoxic and non-neurotoxic ones. Our studies began from this simple question. We measured some physicochemical characteristics of analogues, which are commonly used in such studies, i.e., log P, q_1, and q_2, the electron densities of the C_1 and C_2, k, the bimolecular rate constant of analogues with reduced glutathione and oral LD_{50} values. Using these parameters we tried the discriminant function analysis to divide these two groups of analogues and we obtained a simple function, $y = -3.64 \log P - 346\ q_2$ ($P < 0.01$), suggesting that the neurotoxicity depends greatly upon these two parameters. Although this function does not tell the real mechanism of the neurotox icity, calculating these two parameters may help to predict neurotoxicity of new analogues of unknown nature.

The next approach was to understand the acute toxicity of acrylates and methacrylates. In this study we used a multiregression analysis according to the model first proposed by Hansch and Fujita. In this model they used lipophilicity and electron density, both important parameters determining biological activity of chemicals. In our study we again measured log P, k and LD_{50}. Using these values we obtained the best fitting regression equations for acrylates and methacrylates. For the former we found that oral LD_{50} values were well correlated with log P, but for the latter the correlation coefficient was lower than the former as shown below.

$$\log (1/LD_{50}) = -0.423 \log P - 0.735 \quad r = -0.9909 \ (P < 0.05)$$

$$\log (1/LD_{50}) = -0.412 \log P - 1.562 \quad r = -0.795 \ (P < 0.05)$$

The next study is the structure-activity relationship of monoaliphatic nitriles. Some nitriles are known to be toxic because of their liberation of cyanide ions in the body, but some are also known to be less toxic. We studied their acute toxicity with special reference to the cyanide liberation and structure. We again measured LD_{50} and log P of each compound. After the regression analysis we obtained two equations, one parabolic and one linear and found that the compounds fitted in the parabolic function liberated more cyanide ions than the linear one, and we tentatively named these compounds respectively as group 1 and 2. The group 2 compounds exerted their acute toxicity with less cyanide liberation, probably with their own biological activity. We are now studying the mechanism of their actions.

The last study is concerned with the acute toxicity of monoketones and their structures. This time we measured LD_{50} under the control and carbontetrachloride (CCl_4) pretreated conditions, and log P of test compounds. The scatter diagrams between LD_{50} under the two conditions and log P fit well into parabolic curves. The regression equations for control and CCl_4-pretreated LD_{50} showed good correlation with high significance as shown below.

$$\log (1/LD_{50})\ \text{Cont} = -0.120 (\log P)^2 + 0.417 \log P - 1.743$$
$$r = 0.946 \quad P < 0.01$$

$$\log (1/LD_{50})\ CCl_4 = -0.103 (\log P)^2 + 0.462 \log P - 1.660$$
$$r = 0.884 \quad P < 0.01$$

These results may indicate that the acute toxicity of monoketones depends greatly on the log P with an optimal value, and exert toxicity by their parent compound, not by their metabolites, because the CCl_4-pretreated LD_{50} was always smaller than the control LD_{50}. If the metabolites produced toxicity, the LD_{50} values should have been larger, since CCl_4 inhibits the metabolism of monoketones in the body.

Summary

In summary, we have shown our studies on the structure-activity relationship of some industrial chemicals. As shown earlier, these studies neither tell you the biological effects nor the mechanism of action of each compound, but in vitro measurements or calculations of physicochemical parameters of a chemical group could give various information about their biological activities. Toxicological studies so far have been made mainly by biologists and medical people, but in future, more contributions from chemists as well as physicists in this area will be of value. Cooperation of these people may promise a better understanding and prediction of toxicity of new chemicals.

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AN EVALUATION OF THE RELATIONSHIP BETWEEN THE ACUTE IRRITANCY POTENTIAL OF TOPICALLY APPLIED CHEMICALS IN THE RABBIT AND MAN

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Abstract

The irritancy of 12 chemicals was assessed by their topical application under occlusive patch tests in multiple concentrations using a block design to 12 New Zealand white rabbits. The chemicals were left in place 24 hours. Scoring for the presence or absence of irritation was carried out at 48 hours. A mathematical model was constructed using a computer assisted model building system relating the proportion irritated to the topical concentration and an irritancy co-efficient for each chemical. The irritancy of the chemicals was evaluated in 12 human volunteers who were exposed to the chemicals under closed patch tests for 6 hours with the sites read one hour after exposure for evidence of irritation. Human and rabbit relative irritancy potential proved to be correlated for acute irritant effect. The acute irritancy co-efficient was not correlated with human repeated insult patch test scores. The rabbit using this model is a valid predictor of acute human irritancy potential but does not predict chronic human irritancy potential.

Key Words: predictive tests, acute irritant contact dermatitis, acute irritancy potential.

Résumé

Le pouvoci irritatif de 12 produits chimiques a éte évalué par l'application topique de diverses concentrations des vites substances, ("Patch test") sur des lapins blancs de Nouvelle-Zelande.

Les agents furent laissés en place pour une periode de 24 heures. La lecture des résultats fut faite à 48 heures.

Un modèle mathématique informatisé fut employé grâce auquel une relation fut établie entre la dimension de la zone irriteé et la concentration du produit. Un coefficient irritatif pour chacun de ces agents fut ainsi établi.

Le pouvoir irritatif de ces mêmes agents fut également évalué sur 12 volontaires humains, lesquels fureut exposés selon la même technique pour une période de 6 heures. La lecture des résultats fut faite une heure aprés la fin de l'exposition.

Le pouvoir irritatif s'est avéré être le même eu ce qui concerne la réaction irritative aigue eutre le lapin et l'humain. Toutefois le coefficient irritatif ne s'est pas prouvé être valable dans les cas d'exposition répétées chez l'humain.

Le modèle employaut le lapin est un bon moyen de prédire le potentiel irritatif aigu chez l'humain mais ne prédit pas adéquatement le potentiel d'irritation chimique.

Introduction and purpose

Irritant contact dermatitis is the most common exogenous cause of eczema (1). Resulting from the direct noxious effect of a contactant on the integument, in contrast to allergic contact eczema where the host immune response is the most important factor, this common disorder has spawned predictive tests for the evaluation of the irritant effects of chemicals that may come into contact with human skin. The technique for evaluation of the irritant effect of chemicals on the skin of rabbits developed by Draize et al. (2) has been in wide use for many years. Steinberg et al. (3) demonstrated that the latter method does not accurately predict the irritant effect of subacute exposure to the same chemicals in human predictive tests. The purpose of this article is to present the results of a modification of the acute irritancy protocol developed by Draize et al. which is based on a previously reported human predictive technique developed by Kligman and Woodring (4). This investigation involved the use of multiple topical concentrations and the scoring of the threshold irritant concentration in contrast to the scoring of the degree of the irritant reponse used by Draize et al. (2). This method was utilized to avoid possible variability in the interpretation of responses which has been reported to occur with the protocol of Draize et al. (2). Steinberg et al. (3) found the standard Draize protocol to be a poor predictor of human repeated insult response. It was hoped that this modification of the methodology might improve the predictive capability of the rabbit model.

Materials and Method

Chemicals

The chemicals used in this study are outlined in Table 1. Each was prepared using four or more concentrations exponentially related to one another with the concentrations of all 12 overlapping throughout the array as noted in Figure 1.

The specific ranges were based on previously reported threshold irritancy concentrations (4-9). Concentrations were chosen to range from one unlikely to produce irritation to one likely to do so.

TABLE 1: Chemicals Used in Tests and Their Respective Assigned Symbols

Assigned Symbol	Name
A.	Dowco 214, 0,0-dimethyl-0-3,5,6-trichloro-2-pyridylphosphorothioate, technical grade, powder
B.	Propylene Glycol, USP
C.	Salicylic Acid
D.	Benzoic Acid
E.	Triethanolamine
F.	Benzalkonium Chloride
G.	Formaldehyde
H.	Sodium Lauryl Sulfate
I.	Naled or Dibrom, dimethyl-1,2-dibromo-2,2-dichloroethyl phosphate, technical grade
J.	Diethyltoluamide (DEET), technical grade
K.	Ethanol
L.	Distilled Water

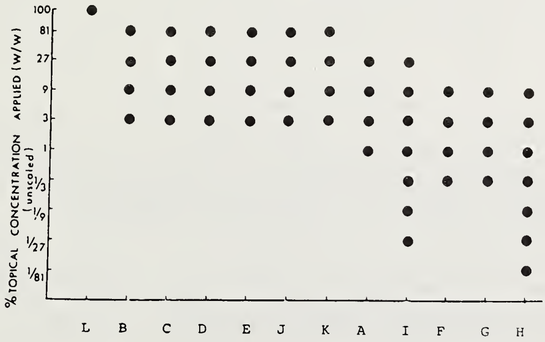


Figure 1: Concentrations of Chemicals Used in Animal Patch Tests

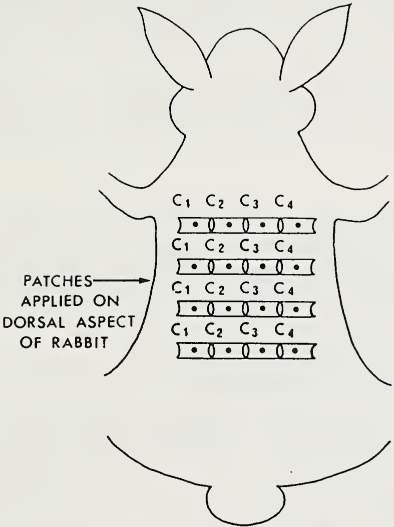
The chemicals were formulated in either petrolatum, a water-oil emulsion (glaxal base, Glaxo Laboratories, Toronto, Canada) or anhydrous eucerin, USP. It was necessary to use different vehicles because of varying chemical properties of the substances utilized to ensure that a homogenous product for topical application was produced. Dr. Howard Maibach kindly assisted in the procurement of several of the chemicals which have been used in previous investigations (3,5).

Animal investigation

Twelve New Zealand white rabbits were obtained from Goddard Rabbitry, Mount Albert, Ontario. The 12 rabbits were divided into three sets of four rabbits which received the same topical application which will now be described. The animals were housed in separate metal cages and fed Purina Rabbit Chow and fresh water "ad libitum". The shoulder to flank skin of each rabbit was clipped with an Oster animal clipper (Oster Corporation, USA). Four sets of 4 test patches were placed on each animal as outlined in Figure 2. Chemicals were divided into four groups and applied as groups (ie., G_1, G_2, G_3 or G_4) on one rabbit. The groups were arranged in an overlapping fashion to facilitate later statistical analysis as follows:

Group	Chemicals
G_1	A B C D
G_2	D E F G
G_3	G H I J
G_4	J K L A

Chemicals in group G_1 were applied to "Al test strips" (Hollister-Stier Limited, Toronto, Canada) and placed on the back of rabbit #1. The strips were fixed to the back with "Scanpor" tape (Hollister-Stier Limited, Toronto, Canada) and the animals' torsos were then wrapped with 7.5 cm wide "Elastoplast" tape (Smith and Nephew, Co. Ltd., Toronto, Canada) which was used to secure the patches firmly in place. Figure 2 illustrates the placement of the patch tests. Assigned rabbit #2 in each of the three sets had the G_2 chemicals applied while rabbit #3 had the G_3 chemicals applied and rabbit #4 had G_4 applied. The patches were removed after 24 hours and the sites were examined for evidence of irritation at 48 hours.



Note: concentrations increase from C_1 to C_4 in all cases; all single strips of patches represent one chemical; all 4 chemicals represent one group, G_i.

Figure 2: Schematic of Patch Positions on Rabbit, Illustrating Anatomical Positioning and Grouping of Chemicals and Their Concentrations

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Further tests were not performed for two weeks to allow any irritant effect to subside at the test sites. If any sign of irritation persisted in a particular area at two weeks then that site was avoided in further testing. Rabbit #1 in each of the three sets was patch tested in an identical fashion as described above, except that it was treated with the G_4 chemicals with the repeat testing while rabbit #2 was tested with G_1 chemicals and rabbit #3 with the G_2 chemicals. This rotatory system was employed using four consecutive applications over an 8 week period.

A site was considered to be irritated if there was any sign of redness, edema, or more severe cutaneous reaction. The sites were examined by three observers independent of one another. No attempt was made to quantify the intensity of irritation. A reaction was considered positive if two of the three observers thought it to be so.

This type of chain block design was balanced so that differences between test chemicals were not compounded by differences between animals while the linking of the same chemical tested at different times served to remove any effects of time differences from the comparison of chemicals. The proportion of animals irritated by each chemical at each concentration were tabulated for statistical analysis.

Human investigations

Five males and seven females had the 12 chemicals tested in the rabbits, all at 3% w/w concentration in the same vehicle which had been used in the animal test, applied under "Al test" strips (Hollister-Stier Limited, Toronto, Canada) to the skin of the upper back with "Scanpor" tape (Hollister-Stier Limited, Toronto, Canada). The patch test sites were randomized to eliminate the site of application as a factor in the responses and they were left in place for 6 hours. The sites were examined for evidence of reaction one hour after the patch tests were removed.

Results

There was no significant difference in the proportion of animals irritated at given topical concentrations of each chemical in successive trials throughout the eight week period. The site of application also did not significantly effect the proportion of animals irritated.

The proportion of animals responding at given topical concentrations was analysed using a linear logistic model where p, the probability of an irritant response, after a log odds transformation, was related to the concentration (c) of the specific chemical tested. The log odds transformation was made in the model by taking the natural logarithm (log) of the proportion of animals reacting over the proportion not reacting. Using analysis of variance for data consisting of counts or proportions, the latter parameter was found to be linear in distribution. Using the "GLIM" statistical model building system developed by the Royal Statistical Society (10) the data was directly modelled in terms of the proportions of responding animals. The reactions of individual patch tests were treated as independent; carry-over effects from one patch test to another or from one chemical to another over the time were assumed to be small. The log odds ratio was estimated or "fitted" using a model which involved concentration and a co-efficient of irritancy, d_i, which can be described by the following relationship.

$$\log p/1-p = K \log C + d_i$$

The co-efficient of concentration, K, derived from this experiment has a value of $2.171 \times 10^{-2} \pm 4.861 \times 10^{-3}$ (mean ± standard error) for the 12 chemicals. There was an association of irritant effect and concentration (P 0.05). The K value will change with differing combinations of, or different chemicals. K can be ignored when ranking chemicals for irritancy, as it is a constant for the whole group of chemicals. The estimates of d_i are noted in Table 2, chemicals with the most positive values have the greatest irritancy potential. Benzalkonium chloride proved to be the most irritant while distilled water was the least.

TABLE 2: Irritancy Co-Efficient for 12 Chemicals

Chemical	d_i + Standard Error
A.	-0.8709 ± 0.2222
B.	1.4410 ± 0.4508
C.	0.8073 ± 0.3755
D.	-2.4950 ± 3.3634
E.	2.2190 ± 0.6056
F.	3.0660 ± 0.7196
G.	0.9728 ± 0.2332
H.	0.9538 ± 0.3250
I.	0.4941 ± 0.3037
J.	-2.9920 ± 0.4144
K.	-0.3534 ± 0.3279
L.	-4.1459 ± 0.4364

Note: Positive and negative values do not indicate anything other than relative values.

Steinberg et al. (3) and Phillips et al. (5) conducted modified "Draize" tests as well as 21-day continuous patch tests on humans and rabbits using the 12 chemicals investigated herein. No correlation was found between the data of the previous investigators for repeated human exposure and the d_i values derived from our experiment using the Spearman rank correlation test (11). When the proportion of humans reacting to each of the 12 chemicals after 6 hours of exposure under occlusion in this investigation were paired with the results of the animal investigation for analysis using the Spearman test (11) a significant correlation between the animal and human ranking was present ($r_s = 0.71$, P 0.05).

Comment

Substances studied in this investigation were chosen on the basis of previous studies carried out by other investigators (3,5). Although it was hoped that this type of evaluation of irritancy would prove to be more useful as a predictor of human response than the protocol developed by Draize et al. (2), the derived irritancy co-efficient values do not predict human response in subacute exposure in repeated insult human patch tests. The results do relate to acute human irritant response as shown by the positive correlation between the human and animal data in the present experiment. This suggests that the rabbit used in an acute exposure protocol such as this or the one developed by Draize et al. (2) is a poor predictor of human irritant response to subacute exposure as demonstrated by repeated insult patch tests. This result thus cannot be explained solely by variability in the scoring of responses in the animals as the altered methodology used in this experiment did allow the prediction of acute human irritant reactions. Rather, it suggests lack of predictive value of this protocol and that developed by Draize et al. (2) may be explained simply by stating that it is inappropriate to use an evaluation of an acute cutaneous toxic response to predict a subacute one. The present protocol may prove to be a useful predictor of acute human irritant response, but whether it is a better predictor than the protocol developed by Draize et al. (2) requires further comparative investigation.

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LONG-TERM EFFECTS OF ORGANIC SOLVENTS

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Introduction

Organic psychosyndrome caused by occupational exposure to organic solvents is well known as a temporary dysfunction of the brain due to acute narcotic effects. Epidemiologic studies using case-referent, historic cohorts and cross-sectional methods have also given evidence for chronic solvent-induced mental disorders among exposed workers (1,2,3,4). Mental disturbances are reported such as neurasthenic symptoms resembling psychoneurotic and depressive states (5,6,7). Further evaluation of these patients has shown a clinical picture comparable to a mild chronic organic psychosyndrome (8,9,10,11). The large variation in psychopathological symptoms among exposed individuals makes an extensive differential diagnostic evaluation essential (12). The consequences of the diagnosis are extensive not only for the disabled worker and his family but also for his fellow workers and the employer. The highest possible specificity in diagnosis is therefore necessary and the combination of findings with clinical, psychometric and neurophysiologic methods is needed for the diagnosis of solvent induced chronic organic psychosyndrome.

Regional cerebral blood flow (rCBF) has been demonstrated to be of great value for the differential diagnosis of organic brain diseases causing dementia (13, 14). The aim of this study was to determine the rCBF in workers exposed to organic solvents and to relate the findings to psychiatric ratings, neuropsychological test performance and the results of computed frequency analysis of EEG.

Material

The exposed group (E-gr) comprised 50 male workers aged 27-64 years, mean 42 years. They did not suffer from any known disease and had been exposed to organic solvents in a paint producing plant during 5-46 years, mean 18 years. The exposure consisted of a mixture of the solvents acetone, butanol, butylacetone, ethanol, ethylacetate, white spirit, methl-isobutylketone, toluene and xylene. Assessment of exposure levels for each subject was done by interviews with the workers and by reviewing past records about air concentrations of solvents in similar working places. Summarized exposure for each individual was calculated as a dose index:

$$DI = \sum_{o}^{i} year_i \times HE_i .$$

The hygienic effects (HE) variable was calculated as:

$$\sum_{o}^{j} conc_j / TLV_j$$

using Swedish threshold limit values from January 1982. DI had a range of 1-68, mean 16. The reference group (NE-gr) consisted of 50 healthy male workers from a sugar refinery. They had not been professionally exposed to solvents. Each referent subject was matched to an exposed subject according to age and educational level.

Methods

Clinical examination

A complete medical, social and occupational history was taken. Specific attention was paid to diseases with possible influence on the nervous system and to present status of mental health. Detailed information was taken about smoking and drinking habits and use of drugs. Blood and urine samples were analyzed for evaluation of bone marrow, liver and kidney function. Finally all 100 subjects were given an extensive physical and neurological examination.

Psychiatric interview

By means of a semistructured psychiatric interview 60 psychopathological symptoms (41 reported and 19 observed) were rated in 4 grades. The interview was based on previously used rating scales (15, 16) supplemented with new items constructed for this study. The interview also included a survey of hereditary traits, earlier psychiatric disorders or nervous reactions and current psychosocial factors of relevance for the symptoms presented.

Neuropsychological testing

Nine psychometric tests were used (Table 2). Eight of the tests had previously proved their usefulness in studies of occupational neurotoxicology (4,17). One additional test was the "dots test" based on principles of the Bourdon-Wirsma test. Scores were taken of speed and faults and fluctuations in these variables were calculated. This combination of tests was intended to measure i/general intelligence, ii/verbal and visual memory iii/perceptual speed and accuracy and iv/psychomotor performance.

Regional cerebral blood flow

The cerebral perfusion was determined by ^{133}xenon inhalation technique (13, 18, 19). Each hemisphere was covered by 16 scintillation detectors which recorded the gamma radiation from the diffusible and inert tracer ^{133}Xe. The subjects inhaled the tracer mixed with air for 1 minute followed by 10 minutes of normal air breathing. The rate of isotope washout forms the basis for calculation of flow values. The results presented here will be based on the initial slope index (ISI), and index of the blood flow in the grey matter of the brain. Arterial pCO_2 was estimated from recordings of end tidal CO_2 concentrations.

Electro-encephalograms

Electro-encephalograms were recorded according to international standard with recordings at rest, hyperventilation and photoactivation. During 10 minutes of the recording at rest frequency analysis was made from 4 symmetrically placed electrodes over frontal and parietal areas. Total EEG-power and frequency distribution of power were calculated in all 4 channels. The paper recordings were read visually before the computed analysis was performed.

Statistics

Statistics were calculated on a Univac 1100/80 compute mostly with the program package BMDP.

Results

The medical and social history of each subject revealed n earlier mental disease or severe head trauma in any of th subjects. They had all performed within normal standards a school, in military servide and had steady employment. Thei use of alcohol was moderate with 90% consuming less than 20 g/week and none of them more than 400 g/week. Use o neuro-active drugs was only occasional for 6% and did not occu for the rest. The two groups were very similar regarding thes potentially confounding factors and smoking habits. Clinica examination disclosed no diseases but the exposed group (E-gr had a higher frequency of neurasthenic complaints Statistically significant differences were found for symptoms c tiredness, forgetfulness, irritability, headache, ches oppression and sweating. The E-gr also complained of mor symptoms from the peripheral nervous system like creeping ar numbness in the extremities. There was a trend towards highe frequency of symptoms among the workers who had the highes exposure levels. The psychiatric interview disclosed differences between the groups with respect to heredity f mental disease or alcoholism. Only a few subjects had earli consulted a psychiatrist. Approximately 40% of each group h suffered from short periods of psychic insufficiency due divorce or loss of relative. Actual psychosoci problems were very rare in both groups. The E-gr scored higher on a considerable number of symptoms belonging to the neurasthenic syndrome (Table 1). The NE-gr did not score higher in any symptom. The sums of the ratings of the symptoms listed in Table 1 were significantly correlated with the dose index (Spearman rank correlation $r=0.49$, $p<0.001$) but not to age.

Neuropsychological testing revealed only minor differences between the groups (Table 2). The tests of general intelligence demonstrated the groups to be fully comparable. In nearly all other tests a tendency towards poorer performance in E-gr was disclosed. Analysis of the results of the "dots test" revealed a much slower but also more accurate performance in the highest exposed subgroup possibly indicating compensatory mechanisms. Traditional brain damage diagnostics on each subject found 9 persons in the E-gr with minor deviations from expected performance and 6 persons with a definite indication of mild brain damage. All 15 were among the subjects with the highest exposure. In NE-gr only 4 persons had minor deviations from expected performance (chi square = 8.3 3df, $p<0.05$).

The level of CBF was 4% lower in E-gr with a tendency towards greater difference between the groups at higher exposure levels (Table 3). Analysis of regional flow revealed lower values for the E-gr in all 32 regions measured. The largest and statistically significant differences were detected in the fronto-temporal area of both hemispheres as well as in one parietal area of the left hemisphere. Reduction of flow at older ages was demonstrated in both groups.

Visual reading of EEG's disclosed a clear and statistically significant difference between the groups. In E-gr 18% had an increased amount of ß-waves and 14% had increased δ-θ-activity, compared to 6% and nil in the NE-gr (chi square 11.7 3df, $p<0.01$). These findings were confirmed by the computed analysis (Figure 1). Regional distribution of EEG activity was analyzed as differences between groups in proportions of anterior-posterior power. This procedure revealed that the E-gr had relatively less EEG power in the frontal parts of the brain. The difference was statistically significant on the left hemisphere and the same trend was demonstrated on the right. No right-left differences could be demonstrated in any group.

Discussion

Selection of a proper reference group is crucial especially in studies using behavioral methods like the present one. Pairwise matching and analysis of confounding factors assure good comparability between the groups of the present study. The symptoms reported by the E-gr are fully comparable to the results of other studies (5.6.7). The symptoms could generally be regarded as the neurasthenic symptoms of a mild brain disorder. In the present study we found that the subjects with neurasthenic syndrome had a reduction in functions of attention and that they tried to compensate for this deficit by working slower and with higher accuracy. The subjects increased distractibility due to the organic brain dysfunction can to some degree be compensated in the testing situation where they are allowed to work undisturbed and to concentrate. This may be a reason for the discrepancy found between the symptoms and test performance in the E-gr. The diagnosis of organic brain dysfunction is made by the individual profile of performance on the various tests. These differences could easily disappear when group means of each test are calculated.

TABLE 1: Psychiatric Symptoms with a Statistically Significant Difference Between Exposed and Non-Exposed Groups

	E R %	E<R %	E=R=0 %	E,R=0 %	p-value
Reported items:					
Anxiety	32	2	18	48	<0.001
Worry	36	8	8	58	<0.01
Hostile feelings	34	2	0	64	<0.00
Lability of mood	34	6	0	60	<0.01
Reduced sexual interest	16	0	0	84	<0.01
Constipation/diarrhoea	18	2	0	80	<0.05
Epigastric pain	22	4	0	74	<0.01
Increased sleep	14	2	0	84	<0.05
Headache	30	12	14	44	<0.05
Use of analgetics	34	12	2	52	<0.05
Fatigue	48	2	0	50	<0.0
Concentration difficulties	30	8	0	62	<0.0
Learning difficulties	32	6	2	60	<0.0
Recent memory failure	44	8	6	42	<0.0
Observed items:					
Muscular tension	20	2	0	78	<0.0

Percentages relate to pairwise comparison of rating poin (E-subject higher, lower or equal to NE-subject). P-values based on the binomial distribution.

TABLE 2: Results of Neuropsychological Tests

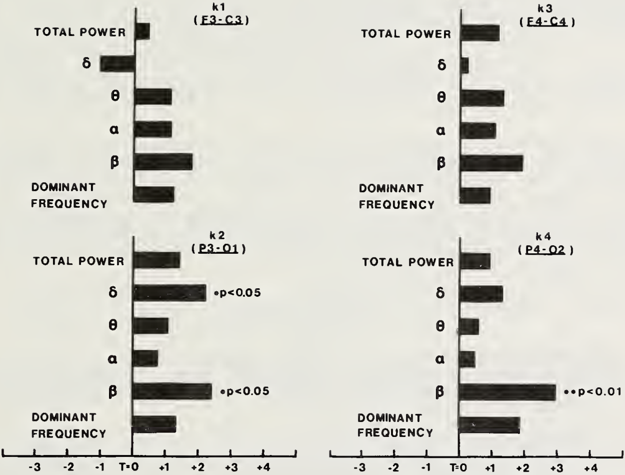
Intelligence	E-gr mean	NE-gr mean	95% confidence limits for the mean difference
Vocabulary	22.1	22.2	−2.7 – 2
Reasoning	21.4	20.5	−0.7 – 2.4
Visual construction	26.3	27.1	−3.6 – 1.9
Memory			
Paired associates	20.8	21.5	−2.9 – 1.4
Benton visual retention test: a) right	7.4	7.6	−0.6 – 0.4
b) wrong	3.8	3.6	−0.7 – 1.1
Perceptual speed and accuracy			
Dots total time	397.8	389.2	−26.2 – 43.5
" time fluctuation	22.8	18.5	1.7 – 7.8**
" total faults	10.1	13.3	−7.4 – 1.2
" faults fluctuation	6.6	7.0	−2.3 – 1.3
digit symbols	53.0	52.2	−4.3 – 5.8
Psycho-motor performance			
Hand motor test	78.0	79.3	−2.5 – 1.2
serial reaction time:			
time interval 1	22.3	21.8	−0.9 – 1.8
time interval 10	23.8	23.7	−1.9 – 2.1

** $p < 0.01$ paired t-test

TABLE 3: Cerebral Blood Flow (ISI) Levels in the Total Groups and in 3 Subgroups with Different Levels of Exposure

		E-group mean	NE-group mean	95% confidence limits for the mean difference
Total	n=50	46.5	49.5	−3.8 – (−0.3)*
Low exposure	n=17	49.4	50.2	−3.9 – 1.0
Medium exposure	n=18	47.4	49.5	−4.7 – 1.4
High exposure	n=15	41.8	44.8	−7.0 – 0.8

* $p < 0.02$ paired t-test
There were no significant differences in arterial pCO_2 between the groups.



Bars indicate Student-t values from paired tests. Positive values indicate greater power in exposed group. K_1, K_3 are frontal and K_2, K_4 are parietal electrodes.

Figure 1: Results of Computed Frequency Analysis of EEF

The results showed a significant correlation between exposure index and symptom ratings and a clear trend of clinical and psychometric findings in agreement with chronic organic psychosyndrome among the highest exposed subjects. The results of the rCBF measurements also indicate an exposure-response relationship between exposure index and reduced flow levels. The slight rCBF reduction is comparable to other reports of flow reduction in solvent-exposed workers (20,21). These findings might indicate an accelerated aging process in the brains of exposed subjects. For individual differential diagnosis rCBF aids in the exclusion of organic degenerative or vascular brain disease. These disorders have distinct and reproducible rCBF patterns facilitating differential diagnosis in each case (14).

Increases in slow δ- and θ-activity and fast ß-activity have earlier been reported to be more frequent among solvent-exposed workers than referent subjects (22,23,24). The computed frequency analysis revealed that this increase is lighter in the frontal region than in the parietal region. This is an interesting observation combined with the greatest reduction of rCBF frontally in the E-gr. The clinical implication of this observation is still unclear and it remains to be confirmed in other studies.

The study has revealed definite differences between the exposed and non-exposed groups. These results using matched referents and careful exclusion of their etiologies to organic brain damage indicate that the organic solvent exposure is a major cause of the observed neurasthenic symptoms and neurophysiological signs of organic brain dysfunction. The exposure effect relationship found for symptoms and rCBF give further support to this conclusion.

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CHRONIC INTRATRACHEAL TOXICITY OF MANGANESE MONOXIDE, MANGANESE DIOXIDE IN RABBITS

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Abstract

Rabbits were given intratracheally Fluoro Carbon-78 suspension of MnO, MnO_2, 5 mg/kg, 1 mg/kg (as manganese), 2 times/month, for a period of 18 months.

The total dose of MnO, MnO_2 were 800 mg/head, 1200 mg/head.

Résumé

Des lapins ont reçu par administration intratrachéale une suspension au Fluoro Carbone-78 de MnO_2, 5 mg/Kg, 1 mg/Kg (comme manganèse), deux fois par mois, pendant une période de 18 mois.

La dose totale de MnO, MnO_2, était de 800 mg/tête, 1200 mg/tête.

L'âge moyen des travailleurs analysés était 37 ans et la durée moyenne de service 15 ans. Chez tous ces travailleurs, les valeurs du cobalt urinaire mesuré par spectrophotométrie et les résultats des examens cliniques, des épreuves en laboratoire et des autres analyses (Rayons-X, EGG, etc.) n'ont indiqué aucun état pathologique significatif d'origine professionnelle. Deux échantillons d'eau potable de la région ont été anlysés, l'un provenant de l'approvisionnement en eau publique et l'autre, provenant de celui de l'usine elle-même; la quantité de cobalt observée était 1 ppb (méthode spectrophotométrique).

For about ten years we have been carrying out a medical surveillance programme on a group of workers at a petrochemical plant working on oxosynthesis, in which cobalt hydrocarbonyl ($HCo(CO)_4$) and cobalt carbonyl ($Co_2(CO)_8$) are used as catalysts.

As with other metals, cobalt carbonyls are formed when, in appropriate temperature and pressure conditions, a gaseous phase containing carbon monoxide (CO) comes into contact with cobalt. Once formed, the metal carbonyls tend to remain in this state only in the presence of CO; they are unstable in air and tend to decompose into CO and metal. The most widely used carbonyls in industry are nickel carbonyl and iron pentacarbonyl which, together with cobalt hydrocarbonyl, are potentially the most hazardous because of their relatively high vapour tension. It has been calculated that the half-life of nickel carbonyl in the air is about 675 seconds, whereas the half-life of cobalt carbonyl is 10-15 seconds. The half-life of iron pentacarbonyl seems to be much longer than that of nickel carbonyl, probably in the order of hours.

Cobalt hydrocarbonyl ($HCo(CO)_4$) is a gas that decomposes rapidly in the air, whereas cobalt carbonyl ($Co_2(CO)_8$) is a crystalline solid with low volatility.

These data, as we will see, support some aspects of the toxicity of cobalt carbonyls, which should, however, be considered much less toxic than nickel carbonyl.

Since there are very few data in the literature on biological monitoring of cobalt carbonyl exposure, we believe our personal experience and the clinical data collected over the observation period may be of interest.

The few reports on the biological monitoring of exposure to cobalt compounds mainly concern processes using cobalt metal or its organic compounds as a binder of ingredients.

Of such processes, the production of hard metals is of particular importance since it is with this industry that the respiratory effects of cobalt, the so-called hard metal disease,

BIOLOGICAL AND CLINICAL MONITORING OF WORKERS OF A PLANT PRODUCING ALCOHOLS WITH COBALT HYDROCARBONYL BASED CATALYST

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Abstract

The paper reports the results of biological and medical monitoring carried out over ten years on workers of a plant producing alcohols (n-butyl, isobutyl and 2-ethylhexyl alcohols), where high grade propylene as well as propane are used as feedstock and cobalt hydro-carbonile is used as a catalyzer.

The results of the environmental measurements of the catalyzer are also reported.

The average age of the workers under study was greater than 37 years and the average length of service was greater than 15 years. In all these workers, the values of urinary cobalt measured by spectrophotometry and the results of clinical examinations, laboratory tests and other investigations (X-ray, ECG, etc.) failed to reveal any significant pathological state of occupational origin.

Two samples of the drinking water of the area were tested, one taken from the public water supply and another taken from the plant's own water supply; the quantity of cobalt found was <1 ppb (spectrophotometric method).

Résumé

Le présent document donne le compte-rendu des résultats des contrôles biologiques et médical effectués sur une période de dix ans chez les travailleurs d'une usine produisant des oxo-alcools (n-butyl, isobutyl et 2-éthyl-hexyl-alcool), où des propylènes de haute qualité de même que du propane ont été utilisés comme oléfines et de l'hydrocarbonyle de cobalt comme cataliseur.

Les résultats des mesures environnementales du cataliseur sont également présentés.

was found in the exposure chamber, the LC_{50} value should be considered as the result of the effects both of cobalt hydrocarbonyl and of its decomposition products. It should, however, be observed that a comparison of the clinical signs and the macro- and microscopic pathology (chemical pneumonia) induced by cobalt and nickel carbonyls leads to the assumption that the acute toxicity of cobalt hydrocarbonyl for experimental animals is about half that of nickel carbonyl (Stokinger, 1972).

In short, the experimental observations seems to lead to the conclusion that the clinical, biochemical, haematological and anatomopathological findings in animals (dogs, rats, guinea pigs) exposed daily for three months to $HCo(CO)_4$ are similar to those previously observed in animals exposed to Co.

The data obtained from animal experiments demonstrate a degree of toxicity that certainly cannot be defined as high. This discrepancy between clinical observations and experimental research may perhaps be due to the fact that since cobalt tetracarbonyl has a strong smell even at very low concentrations, exposed subjects are alerted as soon as the environmental conditions become potentially hazardous. It may therefore be possible that the lack of any findings of health effects in the exposed is due to the rapid decomposition of the hydrocarbonyl and to the low volatility of the carbonyl. In experiments with cobalt hydrocarbonyl, the animals were considered as exposed only to inorganic cobalt as a result of decomposition of the hydrocarbonyl.

The technological oxosynthesis cycle exploits the hydroformylation reaction, which can be expressed as:

$$R\text{-}CH{=}CH_2 + CO + H_2 \longrightarrow R\text{-}CH_2\text{-}CH_2\text{-}CHO$$

Thus, starting from an olefin with n carbon atoms, an aldehyde with n+1 carbon atoms is formed; the aldehyde is then hydrogenated to an alcohol which is in the final product of oxosynthesis:

$$R\text{-}CH_2\text{-}CH_2\text{-}CHO + H_2 \longrightarrow R\text{-}CH_2\text{-}CH_2\text{-}CH_2OH$$

These are primary alcohols which are used in the manufacture of PVC plasticiters including phthalates of n-butyl, isobutyl and 2-ethylhexyl alcohols.

The olefin used in the plant is high grade propylene (over 90%) to which propane is added to make up the remaining percentage. The reaction between propylene and synthesis gases, which is catalyzed by cobalt carbonyl, takes place at equilibrium between cobalt carbonyl ($Co_2(CO)_8$) and cobalt hydrocarbonyl ($HCo(CO)_4$). Cobalt carbonyl is obtained starting from cobalt (in the form of $Co(OH)_2$ powder in suspension with dry butanols) and from carbon monoxide (CO) are associated. The pulmonary fibrosis that characterizes this disease does not seem to be solely due to cobalt but also to other metals used in the technological process, such as tungsten, titanium carbide, tantalum carbide and cobalt or tungsten carbide and cobalt, according to the type of alloy.

Other occupational health effects of exposure to cobalt are polycythemia of varying degree due to oral absorption of cobalt at doses of about 2.0 mg/kg, and allergic dermatitis due to skin contact with Co dust and other cobalt compound dusts. These haematological changes are clearly the most evident expression of the stimulating action of cobalt (which is an integral part of the cyanocobalamin molecule - Vitamin B_{12}) on the haemopoietic system. However, cobalt deficiency more frequently produces anaemia in animals than in man, for whom the requirements are minimal (only traces).

Other effects due to the action of cobalt on the human organism include the characteristic "beer drinkers' cardiomyopathy" consisting essentially of a degeneration of the myocardiac fibres that has been ascribed to the effect of cobalt added to beer (up to 1.2ppm) as a foam stabilizer (in the form of ionic cobalt, probably in association with alcohol (Morini and Caniel, 1967). The clinical signs of cardiomyopathy observed in Canadian and Belgian beer drinkers were: rapidly evolving right and left cardiac decompensation, heart enlargement, pericardial effusion, galloping heart rate, hypotension and shock (Alexander et al., 1972). The cardiomyopathy is sometimes reversible and can be reproduced in experimental animals.

Data on the toxic properties of cobalt carbonyls come almost exclusively from experimental research, since there are no reports in the Western literature of human effcts due to industrial exposure. As far as we know, the only reports concerning occupational intoxications come from the USSR (Kalekivi, 1970), where both acute and chronic intoxications were observed in workers employed in the production of butyl alcohol by oxosynthesis.

In the cases of acute intoxication that occurred following exposure to cobalt octacarbonyl, respiratory changes were observed, with bronchospasm, focal infiltration in the lung, dysproteinemia, neutrophilic leukocytosis, etc. Chronic intoxication was characterized by a moderate increase in erythrocytes, reticulocytes and leukocytes, in cholesterol, prothrombin, bilirubin, total proteins, albumin and fibrinogen; symptoms attributable to functional changes in the respiratory apparatus and Central Nervous System were also observed.

The LC_{50} for 30 min exposure to cobalt hydrocarbonyl in the rat is approximately 165 mg of Co/m^3 (Palmes et al., 1959). Since in these experiments, less than 10% hydrocarbonyl

present in the synthesis gases. The conditions at which cobalt carbonyl is obtained are characterized by elevated pressure ($>$ 400 kg/cm^2) and temperature ($>$ 180°C).

Formation of aldehyde occurs at a pressure between 300 and 400 kg/cm^2 and at a temperature of 185°C. The quality of the products is influenced by the process temperature. Thus, for example, for production of n-butyraldehyde the reaction temperature must be kept lower than for i-butyraldehyde in this way the n-butylaldehyde/i-butyraldehyde ratios are higher and there are greater aldehyde yields, with consequent reduction of byproducts and processing residues. When the reaction is completed the pressure drop causes decomposition of cobalt carbonyl and formation of Co and CO. Co is attacked chemically with H_2SO_4 and returned to the catalyst recovery section, where the suspension of $Co(OH)_2$ in dry butanols is regenerated. CO is eliminated with other vent gases via the general plant exhaust network. The aldehyde which, following a preliminary distillation, has already lost some of the residues, is then further distilled to eliminate any byproducts still present.

In the next operation, butyric aldehydes are separated into iso-aldehyde and normal aldehyde and then stored. With the separation of the isomers, the continuous cycle of isosynthesis is completed and subsequent operations are organized in cycles, including hydrogenation and refining phases, with cycles on isobutanol, n-butanol and 2-ethylhexanol.

2-ethylhexanol is prepared in a separate section where aldolic condensation takes place with subsequent dehydration of n-butyraldehyde (two molecules of n-butyraldehyde give one molecule of EPA (ethylpropylacrolein) plus one molecule of H_2O). EPA is then hydrogenated in the same way as other aldehyes, i-butyraldehyde and n-butyraldehyde, produced at the plant. Hydrogenation of aldehydes is performed in the vapour phase under pressure in catalytic converters at a tempoerature of about 150°C.

The hydrogenation converters are tube bundle types with a nickel-based catalyst.

The H_2 comes from a chlor-alkali electrolytic plant. The alcohols obtained from hydrogenation are then refined and stored.

The workers at our plant can be exposed to cobalt carbonyl in the following areas involved in the operating cycle:

- compression and reaction
- decobalting
- aldehyde distillation
- preparation of catalysts

In these areas, the environmental concentrations of cobalt measured periodically with atomic absorption spectrophotometry were on average below the ACGIH (see below) proposed limit values, with exceptions mainly in the catalyst loading area and cobalt filter area, where occasionally cobalt concentrations reached values of 2.3 and 1.9 mg/m^3 for short periods.

Similar results were obtained for determination of carbon monoxide in the areas of the plant where pollution may occur (see description of technological cycle).

Occupational exposure limits for cobalt carbonyl have not yet been fixed in a final form. The national contract for chemical workers in Italy recognizes the ACGIH (American Conference of Governmental Industrial Hygienists) values, and in the "Notice of Intended Changes" for TLVs adopted for 1982, the ACGIH lists the following cobalt compounds:

– cobalt carbonyl, as Co	0.1 mg/m^3
– cobalt hydrocarbonyl, as Co	0.1 mg/m^3
– cobalt metal, dusts and vapours, as Co	0.05 mg/m^3

It is proposed to reduce the limit of metallic Co from 0.1 to 0.05 mg/m^3 because pulmonary changes have been observed in animals after only 3 months' exposure to a concentration of 0.01 mg/m^3 (Kerfoot et al., 1975).

The group under medical surveillance consists of 59 workers (mean age: 40.4 years, average length of service: 13 years) working in an open-air plant located on the eastern sea coast of Sicily. The local climatic conditions are such that there is frequent natural ventilation, which means that good envirnmental conditions can be maintained, since any occasional leaks of toxic substances from the plant are dissipated and do not create hazardous situations for the workers involved.

For the 59 subjects under study, measurement of urinary cobalt is performed as well as a periodic medical examination, plus a number of laboratory tests (haematologic and enzymologic), and other tests (spirometry, electrocardiogram, etc.). From time to time, at the discretion of the plant physician, other tests may be carried out on the basis of the results of the medical examination.

Table 1 gives the concentration of urinary cobalt (mean and standard deviations) year by year for the 59 workers in the period covered by our study (1973 – 1981). The values are corrected to a specific gravity of 1.024 and were measured on samples collected at the end of the workday, in view of the fact that it is practically impossible to collect 24-h urine samples in the factory. The trend of the values is shown in Figure 1.

TABLE 1: Mean and Standard Deviation of Urinary Co Values of Plant Workers from 1973 to 1981 (μg/l)

Year	Mean	Standard Deviation
1973	12.49	10.32
1974	8.67	8.13
1975	4.33	3.67
1976	6.03	5.48
1977	4.96	4.29
1978	4.72	4.56
1979	6.38	7.82
1980	3.79	2.79
1981	3.57	3.71

Table 2 shows the concentration of urinary cobalt (mean and standard deviation) in the same time period, but divided according to job. The trend of the values is shown in Figure 2.

The trend of the concentration of urinary cobalt over the years clearly shows that from 1973 to 1981 there was a marked reduction in these values. The reaction may be attributed to both the technical improvements gradually made at the plant and also to a more careful implementation of the personal and general hygiene measures of prevention. The trend, calculated with the least squares method, is significant ($p < 0.05$).

As can be seen from these tables, our workers can be considered as having a very low level of exposure; this can also be inferred from the environmental concentrations measured which, in normal working conditions, are below the recommended standards. The values of urinary cobalt in the workers under study may also be considered as complying with the biological reference standards reported in the specialized literature for cobalt metal and its inorganic compounds.

We do not think that the values of urinary cobalt found especially in recent years, present any risk for the workers, W should like to stress here that although it is not yet possibl to interpret the urinary concentrations of cobalt (and othe metals) in terms of individual risk, the values found in thes workers are nevertheless amongst the lowest of those reported i the literature for occupational exposures (Alexanderson an Swensson, 1979; Barborick 1971; Pellet et al., 1982; etc.).

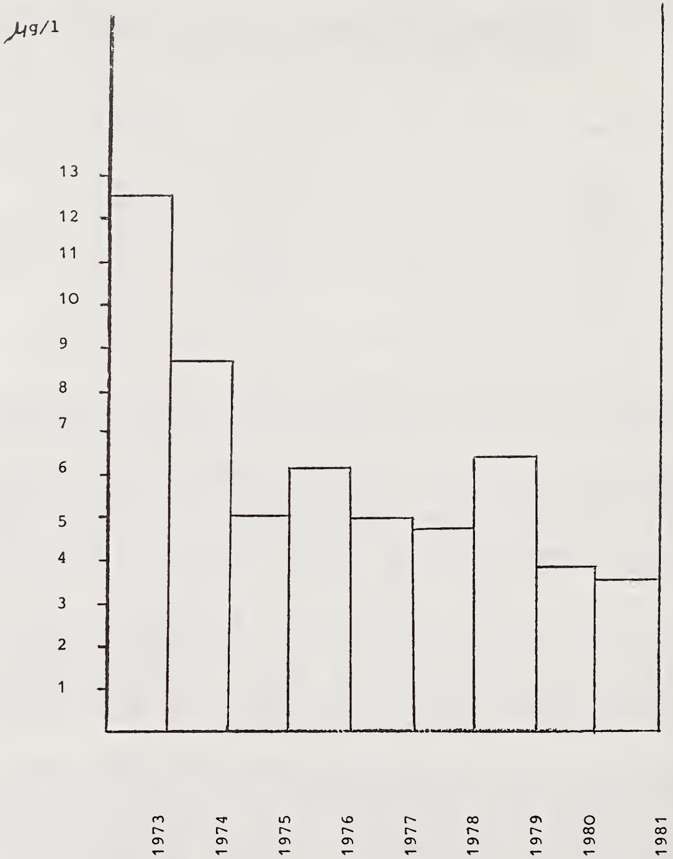

Figure 1: Mean Urinary Co Values of Plant Workers 1973-19781

TABLE 2: Mean and Standard Deviation of Urinary Co Values of Plant Workers over Entire Study Period, According to Plant Area and Job (mg/l)

Job	Mean	Standard Deviation
Desulphurization and reaction	4.71	2.04
EPA - Hydrogenation and refining	6.32	4.22
Aldehyde distillation	6.69	3.46
Catalyst recovery	5.43	3.28
Shift assistant	5.57	2.88
Shift leader	4.65	1.51
Shop steward	4.03	2.41
Shop and group secretary	6.37	3.84
Oxide technology	4.70	1.76
Area mechanic	12.22	4.63

There are wide discrepancies in the literature as regards the levels of urinary cobalt in non-exposed subjects, with values ranging from 0.73 µg/day (Wester, 1973), to 98 µg/l (Schroeder, 1971).

In Italy, values of urinary cobalt between 0.3 and 4.1 µg/24 h have been observed in exposed populations (Clemente et al., 1977); in 25 non-exposed subjects in Sweden mean values of 0.4 µg/l were reported (Alexanderson and Swensson, 1979).

With a view to evaluating the influence that absorption of cobalt with drinking water may have on urinary cobalt, we measured the cobalt concentrations in the two water supplies serving the plant and the surrounding territory where the majority of the workers live. Determinations were made with the atomic absorption spectrophotometric method and in both samples cobalt was lower than 0.1 ppb, which can be considered of no significance.

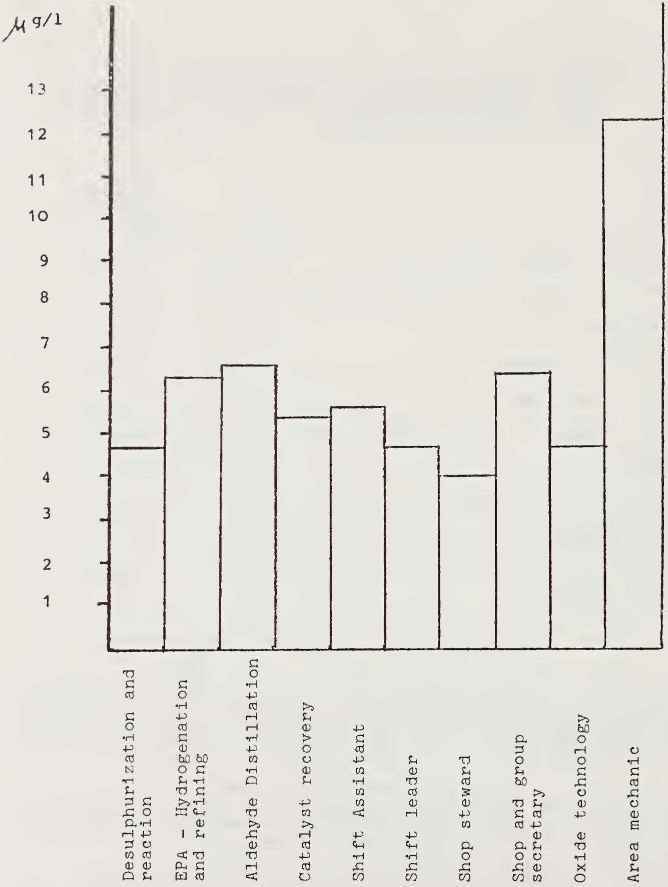

Figure 2: Mean Urinary Co Values in Plant Workers, over Entire Study Period, According to Plant Area and Job

Figure 3 shows the percent incidence of diseases and complaints among the workers under study. The most frequent pathological findings concerned the digestive system, which covered more than 43% of all clinically diagnosed morbid states (diseases of the stomach, intestine and liver, etc., were considered separately for statistical and organizational requirements of the Company). This is a rather high incidence which seems to be related to occupation, although not exclusively.

In the observed cases of liver disease, the main findings were: more or less marked liver enlargement with a usually slight increase in the values of the laboratory tests periodically perfomed at the plant (transaminase, GT, LDH, bilirubin, etc.).

It is, well known that diseases of the digestive system are generally very frequent but are even more so in industrial workers, especially shiftworkers, due to the fact that they cannot have regualr meals, either as regards type of food or mealtimes.

We should like to stress the low incidence of diseases of the upper airways and lungs (considered separately for the same reasons mentioned above), since this finding does not agree with the data in the literature, both as regards exposure to cobalt metal and its inorganic compounds and exposure to carbonyls.

The incidence of other diseases does not differ from that observed in other workers.

Skin diseases, especially the allergic type, and asthmatic symptoms are reported to be relatively frequent in exposure to cobalt and cobalt compounds, but in the group of subjects in our study these diseases were the least frequent.

A small proportion of the diseases included under "miscellaneous" concerned disorders of the ears and eyes.

Clinical examination of the workers has never revealed any blood disease that could be associated with occupational exposure. This was confirmed by periodic blood counts which did however, reveal a few cases of thalassemia, which is endemic in the region.

In view of the reports of cardiomyopathy in beer drinkers which has been attributed to cobalt in beer, the workers under study underwent examination by a cardiologist, with periodic ECG. No evidence of cardiomyopathy was found that could be directly or indirectly attributed to cobalt exposure. Of the 59 workers, only 4 showed alterations of the ECG tracing which were due to supra-ventricular extrasystole in one case, to slight sinus tachycardia in another, and to right branch bundle block in the other two.

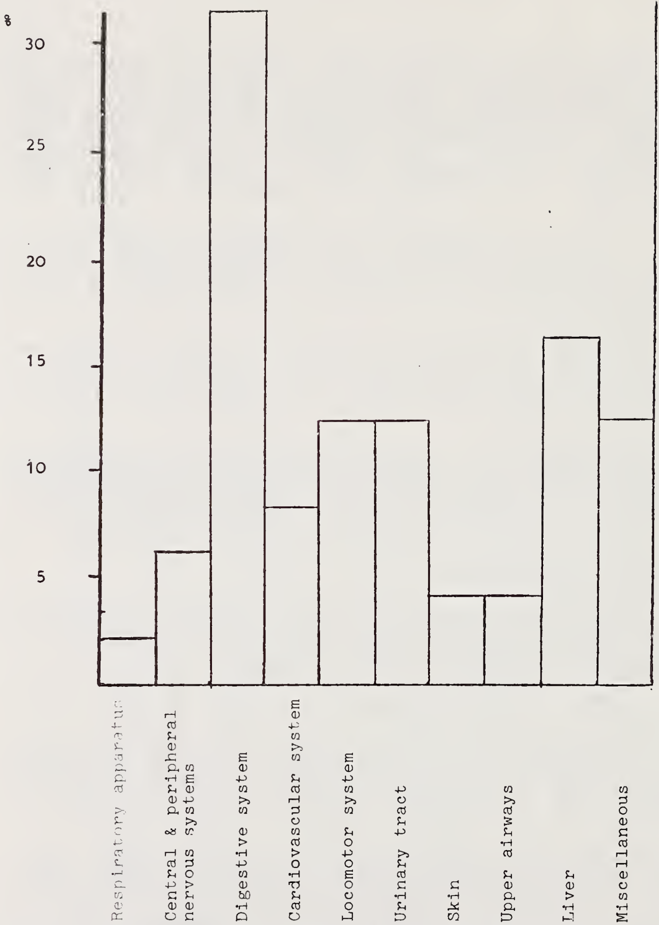

Figure 3: Incidence of Diseases and Complaints among Plant Workers

To conclude, we believe that on the basis of our experience, the occupational risks involved in the technological process described can be prevented with a good industrial hygiene practice and health surveillance of the work force.

The present exposure limits seem to adequately safeguard the workers' health.

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INCIDENTAL UPTAKE OF DIGITALIS AND QUININE IN CHEMICAL WORKERS

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Abstract

Biological monitoring of working environments is concerned almost exclusively with noxious agents. The involuntary intake of drugs has up to now been largely ignored. An examination of workers employed in digitalis production for digitoxin in the serum showed that the levels were at times in the therapeutic range (i.e. between 15 and 30 ng/ml). After improvement of the protective conditions at the work place (improved extraction apparatus, frequent wet cleaning, the wearing of protective clothing and respiratory masks), the values fell continuously to almost zero in the course of the next few months. ECG findings did not show any digitalis effects in any of the cases. Biological monitoring was also used in the quinine production unit first of all by determining the mean quinine concentration on 5 consecutive days (when it was found that values rose from 112 ng/ml on Mondays to 344 ng/ml on Fridays) and later by determination of the total quantity of quinine excreted over 10 days in the urine when it was found that the levels rose during the course of the week from about 300 µg to more than double this level and fell again on Sunday to 98 µg. This was again followed by a rise to more than twice the level. These quantities of quinine are about one third of the excretion that can be found in the urine of healthy subjects after drinking about 700 ml tonic water. The practical importance of biological monitoring of those producing active pharmaceutical ingredients lies in the prevention of complications that might arise when taking medically prescribed drug treatments.

Résumé

Le contrôle biologique des milieux de travail se préoccupe presque exclusivement d'agents nuisibles. L'ingestion involontaire de drogue a jusqu'à présent été grandement ignorée. Un examen des travailleurs employés à la production de digitalis a montré que les concentrations de digitoxine dans le sérum se situait parfois dans la gamme thérapeutique (c.-à-d. entre 15 et 30 ng/ml). Après amélioration des conditions de protection au travail (amélioration des appareils d'extraction, nettoyage humide fréquent, le port de vêtements protecteurs et

de masques respiratoires), les concentrations ont diminué progressivement jusqu'à presque zéro au cours des quelques mois qui ont suivi. Les données ECG n'ont montré aucun effet de digitalis dans aucun des cas. Le contrôle biologique a également été utilisé à l'unité de production de quinine, tout d'abord en effectuant le dosage de la concentration moyenne de quinine calculée sur cinq jours consécutifs (lorsque l'on s'est rendu compte que les valeurs passaient de 112 ng/ml le lundi jusqu'à 344 ng.ml le vendredi) et par la suite en effectuant le dosage de la quantité totale de quinine excrétée dans l'urine pendant une période de dix jours (lorsque l'on s'est aperçu que les concentrations passaient au cours de la semaine d'environ 300 µg à plus du double de cette concentration pour redescendre à nouveau le dimanche à 98 µg.) Cette concentration était par la suite encore plus que doublée. Ces quantités de quinine constituent environ le tiers de l'excrétion dans l'urine de sujets sains aprés avoir bu 700 ml d'eau tonique. L'importance pratique de la surveillance biologique de ces ingrédients pharmaceutiques actifs de production se situe dans la prévention des complications qui pourraient surgir lors d'un traitement avec des drogues prescrites sous ordonnance.

Introduction

The unintentional intake of active substances at the site of production has up to now been paid little attention in the chemical and pharmaceutical industries as the determination of the concentrations of injurious substances in body fluids appeared to be a more important matter. With the availability of more subtle analytical methods that have become available in recent years, this type of biological monitoring should be used more frequently where effects are suspected and at any rate in the determination of pertinent concentrations in the air. Any attempt to lay down acceptable limits, however, will soon reach the extremities of our knowledge because there is scarcely any long-term experience on unintentional intake of active substances or drugs into the human body covering a number of years or decades.

The aim of the present study is to show, by using digitalis and quinine as examples, that even in modern production units where the prescribed safety regulations are observed it is still possible to detect active substances in the body.

We were confronted with this problem for the first time when at the end of 1981 one of the workers in our digitalis production unit was taken ill with persistent "nausea" for reasons that were at first not obvious. The doctor carrying out the treatment decided to investigate whether there was any possible relationship to his workplace and shortly afterwards his serum was examined for digitoxin. A level in the toxic range (66 ng/ml) was found. A first degree AV-block could be seen in the ECG. In a subsequently carried out RIA-test for digitoxin in workers in the digitalis plant who were thought to be especially exposed (a determination was made in each of the workers on four consecutive days) showed that two of the workers had serum levels in the therapeutic range (15 - 30 ng/ml) and in one case the level exceeded 30 ng/ml. The levels in the other workers lay between 7.5 and 15 (once) or below 7.5 ng/ml (six times). 0.0 ng/ml was not found in any of the workers at this time. Furthermore, no symptoms suggesting digitalis toxicity could be found. After intensifying the usual safety precautions in the unit (respiratory protection, air extraction and protective clothing), the investigations were carried out three weeks later on 18 workers in the production unit. It was found that 11 now had levels that were less than half the therapeutic minimum level of 7.5 ng/ml.

Subsequent investigations two and four weeks later did not show any further drop.

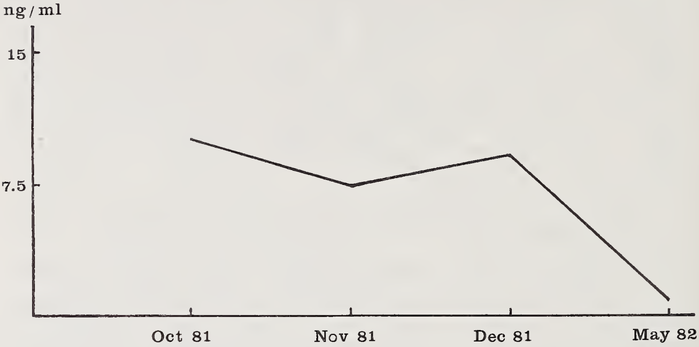
Digitalis lanata also contains digoxin. Its therapeutic serum concentrations are considerably lower than those of digitoxin at 0.5 - 1.5 ng/ml. It was not possible to determine the digoxin ingested reliably as the antibodies used for the RIA-determination also react with digitoxin and other glycosides contained in Digitalis lanata. One can therefore only speak of digoxin equivalents. Concentrations corresponding to 0.6 - 1.15 ng/ml digoxin were found in four workers with the digoxin antibody. In all the others, levels of between 0.0 and 0.5 ng/ml were found.

The last investigation for digitoxin, 7 months after the possibility of action had become known, showed zero values in 8 cases and 8 cases with values between 0 and 7.5 ng/ml. Table 1 shows the time intervals, number of investigations and serum digitoxin levels.

TABLE I: Time Intervals, Number of Investigations and Serum Digitoxin Levels

Date	No. Persons	Means ng/ml	SD	30 ng/ml	15-30 ng/ml	7,5-15 ng/ml	0-7,5 ng/ml	0 ng/ml
Oct/81				1	2	1	6	0
	10	11.61	11.78	10%	20%	10%	60%	0%
Nov/81				0	3	4	11	0
	18	7.45	7.43		16.7%	22.2%	61%	0%
Dec/81				0	3	6	7	0
	16	9.69	6.59		18.75%	37.5%	43.75%	0%
May/1982				0	0	0	8	8
	16	1.09	1.67				50%	50%

The following curve is obtained on the basis of the means for digitoxin at the four examination dates (Figure 1).



After 7 months, therefore, the values approached zero, although the workers in our production unit had continued to work in the plant uninterruptedly for the entire period apart from a 3-week pause at the turn of the year. The digitoxin serum levels following the 3-week pause were, as expected, almost zero. These values were, however, not used in the investigation because the time must be adequate to permit the slowly diminishing digitoxin to disappear completely from the body. Apparently, the usual safety measures and increased motivation of the workers for the use of protective clothing, as had already taken place between October and December, were sufficient to allow the intake of the drug to diminish to almost unmeasurable levels.

The simultaneously recorded ECGs were equally important to us as the detection of glycoside in the serum. A total of 38 ECGs, which were recorded both after several weeks' holiday or absence due to illness as well as after several months' employment in the digitalis unit, did not show any clear digitalis effects in any of the cases. Similarly, there were no clinical symptoms at any time that could be interpreted as toxic digitalis effects.

During the processing of the drug, this can be ingested with the air inspired, through the mouth or through the skin. To determine possible uptake in the inspired air we have carried out technical monitoring in addition to man monitoring, i.e. glycoside determinations in the air of the room. The results permit the deduction that a maximum of about 0.5 - 4 μg total glycosides could be ingested by a person by inspiration over 8 hours. This corresponds to about 1/100 of the daily maintenance dose during digitalis treatment.

Discussion

In the treatment of heart failure, pure glycosides such as digitoxin and digitoxin are used. To monitor therapy, the serum concentrations are determined in the RIA using antibodies which are directed against digoxin or digitoxin. The specificity of these antibodies is, however, limited so that other digitalis glycosides are also determined to a greater or lesser degree. The size of the error can be deduced from the following example. The active serum concentrations of digitoxin are 15 times higher than those of digoxin. The determination of the serum concentration of digoxin can therefore already be biased by digitoxin at concentrations that are scarcely active. Apart from digoxin and digitoxin, the individual extracts and extract fractions contain varying quantities of many other glycosides which also react more or less strongly with the antibody in the RIA. The RIA monitoring of the uptake of digitalis substances during the production of digitalis glycosides is therefore limited in its informative value regarding concentrations.

The first degree AV-block in the worker who caused this action to be started was still detectable several months later after his serum level had already returned to almost zero, so that a cause other than the digitalis action must be assumed for the block.

Quinine

Similar investigations were also carried out for quinine, which has been produced in the Mannheim works since 1859 and in recent years on a large scale.

The substance is still contained even today in many pharmaceutical combination products, but it has lost its earlier importance as a drug for treating malaria. Quinine was in any case unusable for prophylaxis of malaria as its action consisted solely of the inhibition of the development cycle of the malarial parasites in the erythrocytes. The mode of action is thought to be interference with the carbohydrate metabolism of the malarial parasites. Quinine has in addition stimulant actions on uterine muscle and it is also used as an analgesic and antipyretic. After absorption from the gastro-intestinal tract, peak concentrations can be found in the serum about one to three hours later. Breakdown takes place primarily in the liver and only small quantities are excreted unchanged in the urine.

Toxicology

There are scarcely any side-effects on ingestion of about 1 g daily. 3 g or more, however, can cause disorders of vision and hearing. The acute toxicological picture is characterised by headaches, fever, vomiting, excitement, confusion and even unconsciousness. The blood pressure falls and the pulse becomes weak. The lethal dose is about 8 g, but even higher doses have been survived.

Whilst the importance of quinine as a drug has become increasingly less in recent years and decades, its importance as an additive in the drinks industry has continuously risen. A bottle of quinine containing tonic water (0.7 l) contains about 50 mg quinine. After ingestion of this quantity, about 5 mg are excreted via the kidneys in the first 24 hours. Over the next 2 - 3 days, the renal excretion falls rapidly and consists altogether of not more than 13% of the quantity ingested.

There are at present no references in the literature on the unintentional intake of quinine during the course of the production process. We have therefore carried out orienting urine investigations in 17 workers in our quinine production unit to find out, first of all, whether the stages in the process that produce dust cause detectable quantities of quinine to be present in the body. These investigations lasted for 5 days; the workers concerned provided a urine sample in the morning between 8 a.m. and 9 a.m. Drinking of quinine-containing drinks was forbidden on the days before and for the duration of the investigation. 5 comparative investigations in laboratory personnel of our analytical laboratory gave entirely zero values. The 17 urine samples permit the clear conclusion that the highest values in the urine are found on milling, drying and sieving of quinine.

Analysis

The active substance was extracted from the urine samples and was determined fluorimetrically after separation by high pressure liquid chromatography. The analyses were carried out in detail as follows.

The volumes of the 24 hour urine fractions were determined and an aliquot of the sample was stored at -20°C until analysis. 20 µl dihydroquinine (1 mg/l in H_2O), 1 ml 0.1 N NaOH and 5 ml diethylether were added to 1 ml urine in a centrifuge tube with ground glass neck. The mixture was shaken for 10 min and then centrifuged. The ether phase was then transferred to a second test tube and blown to dryness in a thermoblock at 35°C with N_2. The residue was dissolved in 100 µl H_3PO_4 and 50 µl were injected into a HPLC system consisting of an auto-injector (Wisp 710, Waters), pump (Gynotek 600/200) and fluorescence detector (Perkin-Elmer-MPF-3, excitation at 365 nm, emission at 460 nm). The column (25 cm X 3.9 mm) was packed with Nucleosil 10 C-18 (Macherey & Nagel). The mobile phase consisted of methanol/1% H_3PO_4 20/80 (v/v) and the flow rate was 2 ml/min. Quinine standards of 1 mg/l were prepared in the mobile phase. The retention volumes were 9.5 ml for quinine and 12.5 ml for dihydroquinine. The resolution of the two peaks was R = 1.7 (base line separation).

From the following curves it can readily be seen how the quinine concentrations rise form the very low value on Monday to 5-6 fold levels towards the end of the week (the quinine concentrations given in ng/ml represent the mean and standard deviation found for the 17 subjects.

In a second investigation we had 5 workers who worked predominantly in these two sites collect their 24-hour urine for a period of two weeks and the quantities of unchanged quinine excreted were determined. The results of this investigation were very informative. In 3 of the workers the quantities excreted at the weekends and shortly after were clearly lower than before. The maximum quantities found in the 24-hour urine were about one third of that excreted after drinking 700 ml tonic water. These were, however, single recorded peak quantities. On the other days and in the other workers, the excretion was very much lower (on average about 1/5 of the peak values). In this investigation, too, the participants were required to avoid drinking quinine containing drinks.

The following curves show the means and standard deviations of the five persons concerned.

There was a clear increase in the quinine excretion during the course of the week, a fall to lower values at the weekend and then a clear, if not so high, rise afterwards. This possibly shows the better practice of safety measures that accompanied greater consciousness of the dangers.

The urine samples were analysed for the presence of quinidine in addition to quinine. There were very different concentrations both according to days and subject, but without simultaneous serum concentration determinations, such as are usual in the monitoring of quinidine therapy, these results are not directly utilisable.

Possible damage to health that could be associated with the ingestion of small quantities of quinine into the body have not so far been observed. In the monitoring investigations, blood picture and erythrocyte sedimentation rates were determined in addition to the usual laboratory parameters (liver values, creatinine, bilirubin, blood protein bodies, uric acid and lipids). These values permitted, like the intermediate clinical statement, no adverse conclusions. No notable illnesses have been recorded over many decades, although the safety procedures previously were less effective than those nowadays. Finally, quinine-containing drinks, which lead on ingestion to the intake of larger quantities of quinine in the body, are allowed for human consumption in unlimited quantities. But even without any concrete indication of damage to health that could be caused by years or decades of ingestion of these quantities of quinine, we should use the results of these investigations as grounds to remind all the workers to observe the working instructions and to wear the materials for protecting of the body that are prescribed for the respective work place. No other consequences can at present be drawn from these results.

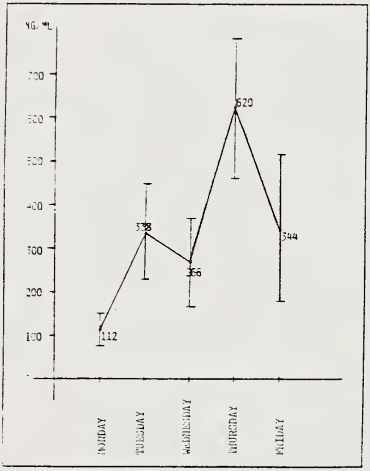


Figure 2: Mean Quinine Concentration in up to 17 Members of the Work Force Measured on 5 Consecutive Working Days

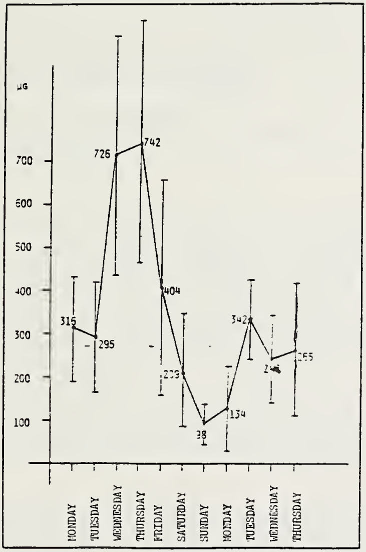


Figure 3: Mean Quinine Excretion in 5 Members of the Work Force Measured on 11 Consecutive Days

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PULMONARY FUNCTION STUDY ON WORKERS WITH LONG-TERM EXPOSURE TO CHLORINE

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Abstract

Forty - eight male workers of a modern chloralkali - electrolysis plant were examined. Their exposure time to chlorine ranged between 10 and 12 years. The average concentration of chlorine in the plant was significantly below the German MAK value (0,5 ppm). The substance has been monitored routinely for many years. Five different pulmonary function tests were made (FVC, FEV_1, TC, FRC, RV). Smoking habits of the workers were considered. Their ages ranged between 34 and 62 years.

The results show that chlorine in low concentration even over a period of more than ten years did not cause any negative influence on the pulmonary functions of the exposed workers.

Résumé

Quarante-huit travailleurs mâles d'une usine moderne de chloralcali-électrolyse ont été examinés. Leur temps d'exposition au chlore variait entre dix et douze années. La concentration moyenne de chlore dans l'usine était inférieure d'une façon significative à la valeur MAK allemande (0,5 ppm); la substance fait l'objet d'un contrôle régulier depuis plusieurs années.

Cinq différentes épreuves de la fonction pulmonaire ont été effectuées (FVC, VEMS, TC, FRC, VR). On a tenu compte de l'habitude de fumer des travailleurs, dont l'âge variait entre 34 et 62 ans.

Les résultats montrent que le chlore en faible concentration, même sur une période de plus de dix ans, ne produit aucun effet négatif sur les fonctions pulmonaires des travailleurs exposés.

Introduction

For many years toxicological and occupational medical interest in chloralkali-electrolysis plants was exclusively focused on the noxious substance mercury. Many studies have been undertaken into the toxicological effect of mercury on different target organs such as the kidney, liver, blood or the central nervous system. The effect of the substance on the CNS has been studied extensively by many authors using various scientific methods, including short-time memory, reaction test, colour determination, both-hand coordination, tremor frequency and nerve conduction velocity measurement.

On the other hand, scant interest has been given to the possible long-term effect of small amounts of the other noxious substance in chloralkali-electrolysis plants, which is chlorine gas.

Only a few American plant physicians and scientists have investigated the question of the influence of chlorine on the workers in chloralkali-electrolysis plants.

Some authors have described a negative influence of the gas in small amounts on lung function parameters of mice and rats.

Chloralkali-electrolysis plant personnel in their activity in the cell rooms may be exposed to small quantities of chlorine gas as well as to mercury vapour present in the plant atmosphere.

In the Federal Republic of Germany the maximum allowable concentration, the so-called MAK-Value for chlorine, a well recognized toxic irritant gas, is 0,5 ppm or 1,5 mg/m^3. In the U.S.A. and a number of other Western countries this value is twice as high.

If one excludes the description of the most commonly occurring cases of acute chlorine gas poisoning, reports on the question of possible long-term effects from the noxious substance in concentrations below the maximum allowable concentrations are few in number. For the most part no data are given on the workplace concentration and furthermore the number of personnel exposed and also the duration of their exposure are usually insufficient to allow any useful pronouncement.

Only the studies by Capodoglio, Wilson or Patil give information on workplace concentration and exposure conditions which allows a comparison to be made within the framework of the question as formulated by us. Here again, however, just as in our own plants, the recorded chlorine exposure data at the workpace are significantly less comprehensive than for the substance mercury. While mercury is measured both by means of fixed collectors and by personal air samplers worn by individuals, the evaluation being based on atomic absorption, the only values that exist for chlorine gas are those ascertained by means of Dräger tubules.

Unfortunately, although this method is quite satisfactory for day-to-day practice, as well as being both simple and low-cost, it only provides evidence as to whether the pollutant concentration is above or below a particular value. Precise values for concentration levels are therefore not possible.

In our chloralkali-electrolysis plants the values recorded over the last four years have been continuously below the German MAK-value of 0,5 ppm - in more precise terms around the detection limit of 0,2 ppm.

Since manufacturing conditions and circumstances in the plants have not altered in any way in the course of the last ten years, we are able to start from the principle that these values for chlorine in the plant atmosphere have applied for that same period of ten years.

• Frequency	monthly
• Place	cell room
• Area	5 different points
• Monitoring System	Dräger tubes
• Results over 5 years	continuously below 0.2 ppm

Figure 1: Air Monitoring Chlorine

Procedure

In selecting the workers to be examined, we started off with persons who have had a minimum exposure time of 10 years. On that basis we gathered together 46 persons in the age range 32 - 62 years (median value 48,3 years). Among workers who had exposure times between 10 and 13 years were 41 native Germans and 5 foreign workers, all from Mediterranean countries (Figure 2).

The 46 persons chosen were subdivided into 7 age groups (Figure 3). Smoking habits and activities in sport were ascertained and enquiries were also made as to pulmonary diseases, such as bronchitis, allergic diseases of the respiratory tract and irritant gas inhalations suffered in the past (Figure 4).

The test subjects then submitted to pulmonary function testing. Four different pulmonary function parameters commonly employed in spirometric mass screening tests were used (Figure 5). In these tests age, height and weight of the persons to be examined were included in the assessment.

1. Number of workers exposed to Chlorine 46

2. Age range 32–62 Mean value 48.3

3. Years exposed Min. 10 Max. 13

4. Nationality: Germans 41

Medit. countries 5

Figure 2: Criteria of the Exposed Workers

Group	Age	Number
I	32 – 35 years	⑤
II	36 – 40 years	⑥
III	41 – 45 years	⑥
IV	46 – 50 years	⑨
V	51 – 55 years	⑧
VI	56 – 60 years	⑦
VII	61 – 63 years	⑤

Figure 3: Age Groups of the Exposed Workers

1. Smoking habits

a) Non smoker	⑰
b) 1 – 12 Cig./day	⑧
c) 11 – 20 Cig./day	⑩
d) over 20 Cig./day	③
e) former smoker	⑧

2. Lung diseases

a) total	⑩
b) allergic	①
c) others (Bronchitis, Chlorine intoxication)	⑨

3. Sports

a) No sports	㊲
b) different sports	⑨

Figure 4: Medical Questionnaire

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1. Forced Vital Capacity	FVC
2. Forced Expiratory Volume/sec	FEV_1
3. Relative FEV_1	$\frac{FEV_1}{FVC}$ %
4. Oscillatoric Resistance	R_{os}

Figure 5: Lung Function Tests

Results

For each of the four pulmonary function parameters the average values in each age group were ascertained. These were contrasted with the applicable norm value for the age group concerned, these norm values having been issued by the Committee of the European Coal and Steel Industry.

Only in age group seven (61-63 years) were the contrasted results marginally lower than the norm value for the parameters FVC, FEV_1, and R.os. In all other age groups the results were better, in some cases distinctly better than the given normal values.

Finally, we compared the group of non-smokers and former smokers with that of smokers. This revealed clearly that the values for the non-smokers were better than those for the smokers for all four parameters. Owing to the relatively small number of subjects, no differentiation on age basis was made in this comparison.

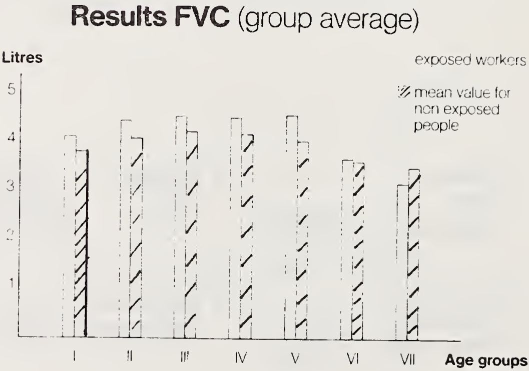
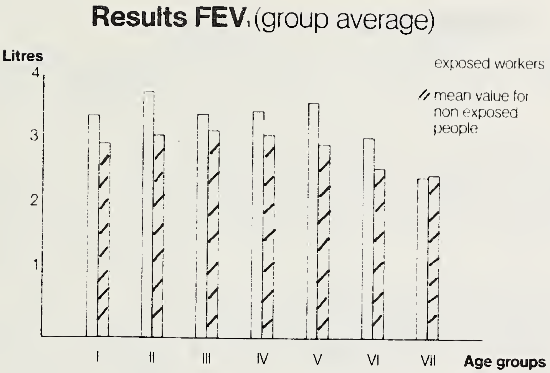


Figure 6



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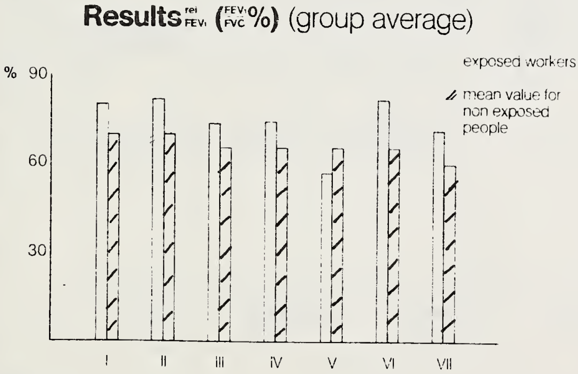

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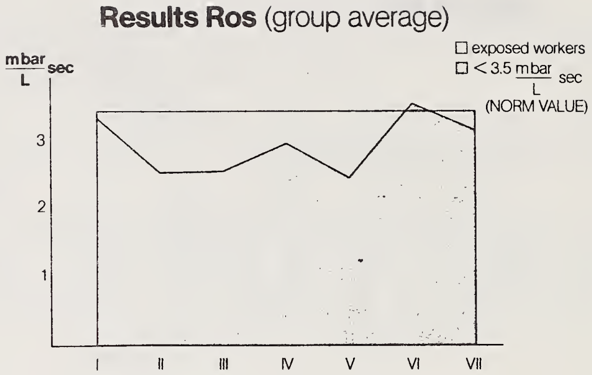

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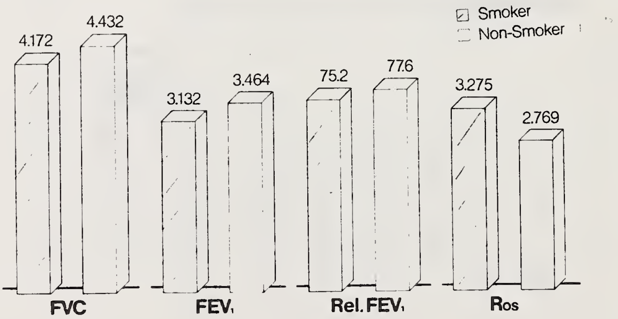

Figure 10

Discussion

The investigations conducted in the chloralkali-electrolysis plant of a modern major chemical company confirm the impressions obtained from the employees under observation because of contact with mercury.

Precise and reproducible analyses of pulmonary function show that no pathological changes are apparent in workers exposed over many years to the harmful substance chlorine in a correspondingly low concentration in the ambient atmosphere. In this context the very slight drop in the values for three of the four parameters in the age group 61–63 years can be termed largely insignificant.

While no impairment was found which could be attributable to chlorine, the poorer results for the pulmonary function of smokers compared to those of non-smokers were clearly apparent. In this connection, too, we find that our results are confirmed in the literature, as for instance, in the investigations conducted by Chester.

Summary

Forty-six chlorine electrolysis plant workers with an average age of 48,3 years and an exposure time between 10 and 13 years were subjected to four different pulmonary function analyses (FVC, FEV_1, relative FEV_1 and R.os.). The concentrations of chlorine, as measured with a Dräger tube at the workplace had remained constant at below 0,2 ppm (MAK value 0,5 ppm) over the previous four years, and it was reasonable to assume this value also for even earlier years. In no age group except that of 61 to 63 years did any of the values measured fall short of the norm values given by the European Communities.

The pulmonary function parameters of smokers were distinctly lower than those of non-smokers.

A FIVE YEAR STUDY OF IONIZING RADIATION EXPOSURE AT A FERTILIZER MANUFACTURING FACILITY

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Abstract

Radiological surveys conducted in 1976 at the phosphatic unit of a fertilizer manufacturing facility indicated the presence of above background levels of gamma radiation near gypsum filters. The radioactive source was identified as radium sulphate which was present in the scale buildup of certain sections of process piping. Radium, a decay product in the uranium 238 series, may be present in phosphate rock in minute concentrations (1-50 pico Curies Radium 226 per gram).

This paper presents the results of a five year monitoring study which was undertaken to determine gamma radiation exposure levels for certain operators working in the phosphoric acid plant. Airborne radon (a decay product of Radium 226) and radon daughter concentrations are given for areas monitored at the phosphatic unit around the site perimeter.

Film badge dosimeters were used to monitor gamma radiation. Film badges were exposed to plant operations for one month before determining the amount of energy absorbed. A direct reading Gieger-Mueler tube detector was used for spot checking area radiation levels. Radon and radon daughter measurements were made using a commercially available detector.

Radiation dose rates, recorded over a five year period, were well below the recommended exposure guideline of 500 millirem per annum for members of the general population. Radon and radon daughter levels were well below the 0.4 Working Level Month guideline recommended by the Atomic Energy Control Board for non-atomic radiation workers.

Résumé

Des études radiologiques effectuées en 1976 à l'unité de produits phosphatés des installations de la fabricatin de fertilisants ont indiqué la présence de concentrations au-delà du mouvement propre de rayonnement gamme près des filtres de gypse. La source radioactive a été identifiée comme étant du sulfate de radium, présent dans l'entartrage de certaines sections de la tuyauterie de transformation. Le radium, un produit de dégration de la série uranium 238, peut être présent

dans la roche phosphatée en très gaibles concentrations (de 1 à 50 pico Curies de radium 226 par gramme).

Le présent document présente les résultats d'une étude de contrôle d'une durée de cinq ans entreprise afin de déterminer les concentrations d'exposition au rayonnement gamme chez certains opérateurs travaillant dans une usine d'acide phosphorique. Les concentrations de radon aéroporté (un produit de dégradation du radium 226) et de radon fille sont données pour les secteurs contrôlés de l'unité de produits phosphatés et ceux qui bordent le périmètre de l'emplacement. Des dosimètres sous forme de pellicules insignes ont été utilisés pour contrôler le rayonnement gamma. Les pellicules insignes ont été exposées aux activités de l'usine pendant un mois avant de déterminer la quantité d'énergie absorbée. Une lecture directe par tube détecteur Gieger-Mueler a été utilisée pour effectuer des vérifications ponctuelles des concentrations de rayonnement du secteur. Les mesures de radon et de radon fille ont été effectuées à l'aide d'un détecteur commercial.

Les taux de rayonnement enregistré au cours d'une période de cinq ans étaient bien en-deçà des directives d'exposition recommandées de 500 millirem pour la population en général. Les concentrations de radon et de radon fille étaient mensuelle suggéré par la Commission de contrôle de l'Energie atomique pour les travailleurs d'un domain à rayonnement non-atomique.

Introduction

Mineral phosphates contain minute quantites (10-20 pico curies per gram) of radioactive material consisting of disintegration products of the uranium 238 series and to a minor extent of the thorium 232 series (Lardinoye et al. 1982). During a routine survey in the fall of 1976, staff of a fertilizer manufacturing facility found certain sections of piping in the Phosphoric Acid Plant emitting above background levels of gamma radiation. These pipes were made of acid resistant material designed to handle filtrate streams from gypsum filters. The radiation source was subsequently identified as radium sulphate ($^{226}RaSO_4$) which had precipitated along with gypsum to form piping scale and sediments.

Wet-process phosphoric acid production

Phosphoric acid production involves reacting sulphuric acid with phosphate rock (calcium phosphate mineral) to produce a slurry of phosphoric acid and gypsum. The slurry is then filtered, separating the acid product from the waste precipitate consisting mostly of gypsum ($CaSO_4.2H_2O$).

$$\underset{\text{(Phosphate rock)}}{Ca_3(PO_4)_2} + 3H_2SO_4 + 6H_2O \rightarrow \underset{\text{(Gypsum)}}{3CaSO_4 \cdot 2H_2O} + 2H_3PO_4$$

The phosphoric acid production process begins by grinding and drying phosphate rock. The fine phosphate rock powder is added to an "attack" tank with sulphuric acid where the reaction proceeds and a slurry is formed. The slurry mixture is then filtered. Gypsum is separated from the slurry and taken to storage. The filtrate containing phosphoric acid is then processeed through evaporators to concentrate the acid product.

The sediments and scale build-up found inside filtrate handling vessels and pipes consist of gypsum and impurities which have precipitated from the acid solution following the filtration. Radium 226 concentrations in the filtrate handling vessels and pipes prompted an investigation to ensure employees were not exposed to significant levels of ionizing radiation. Radium 226 decays to produce radon gas which further decays to solid radioactive elements (daughters). The investigation also involved the monitoring of radon gas and radon daughter levels.

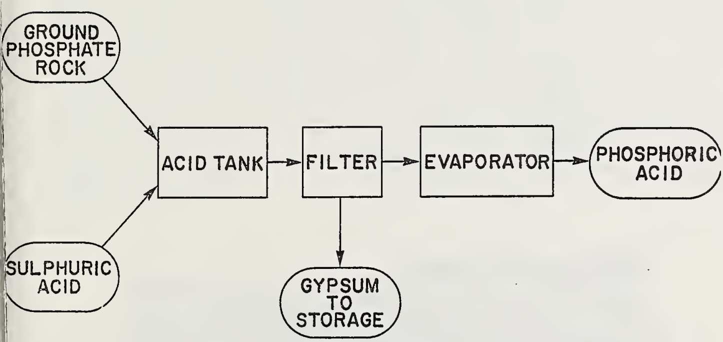


Figure 1: Phosphoric Acid Production

Radiation dose guidelines

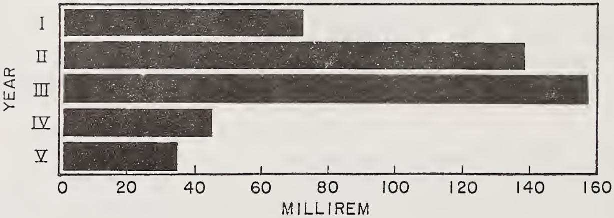
Canada is a member of the International Commission of Radiological Protection (I.C.R.P.), hence, the Commission's recommendations are incorporated into federal and provincial regulations on the use of radioactive materials and x-ray equipment.

The general guideline provided by the I.C.R.P. and provincial and federal governments for an individual member of the general population (non-radiation worker) is a whole body limit of 500 millirem per year (5 millisieverts). This guideline applies to all radiation doses with the exception of medical exposures and normal background exposures. The general philosophy of these agencies is that all radiation exposures should be kept as low as reasonably achievable.

Film badge dosimetry program

In April of 1977, a film badge dosimetry program was initiated at the Phosphoric Acid Plant. The Medical Department proposed the monitoring program to obtain data on longterm employee exposures. This data was used to determine whether there was any significant risk to employee health from exposure to ionizing radiation. Operators of each crew wore a radiation film badge during working hours. Film badges were replaced on a monthly basis. All film badges were sensitive to x-ray, gamma and beta radiation. Exposed films were sent to the supplier for processing and for interpretation of accumulated monthly doses.

Figure 2 shows the mean annual radiation dose for all employee film badges returned. The mean accumulated dose for all crews during Year I was 74 millirem. The mean annual dose in Year II was higher than Year I at 139 millirem. This was due to three particularly high individual readings and to a poor return of exposed film badges during the beginning of Year II. Year III showed a general trend toward increased radiation exposure for all crews. The mean dose for all film badges was 156 millirem. All radiation doses however remained well below the exposure criterion for non-radiation workers.



NOTE: NON-RADIATION WORKER PERMISSABLE WHOLE BODY DOSE IS 500 MILLIREM PER ANNUM

Figure 2: Mean Annual Radiation Dose for all Employee Film Badges Returned

At the beginning of Year IV a major clean-up program was initiated by the Phosphoric Acid Plant to remove accumulated sediments and scale build-up in process equipment. The mean annual radiation dose for Year IV was 46 millirem and well below that reported for any of the previous three years. This trend towards lower radiation exposures continued in Year V. The mean annual radiation dose for Year V was 34 millirem.

Individuals in four job functions were also followed during the five year monitoring program. Data on annual radiation doses for crew leaders, panel operators, tank farm operators and sulphuric acid operators were plotted.

Figure 3 shows the mean annual radiation dose for the crew leader function. In Year I the accumulated dose was 88 millirem. About half of this exposure took place during the first month of Year I. The remaining exposure took place over eleven months following the removal of scale build-up in filtrate piping. The crew leader mean annual dose for Year II was 73 millirem. Average monthly dose levels were between 0 and 30 millirem. Six monthly average dose levels indicated no exposure. Year III showed nearly twice the radiation dose for crew leaders over Year I and Year II. Average monthly dose levels during Year III were between 0 and 34 millirem. Five monthly average dose levels were between about 20 and 34 millirem. There were only three monthly average dose levels which indicated no exposure. Year IV showed a reduction in radiation exposure which was attributed, as mentioned earlier, to a major clean-up of accumulated sediment and scale build-up in process equipment. The trend towards lower radiation doses continued in Year V with crew leaders showing an annual mean dose of 28 millirem.

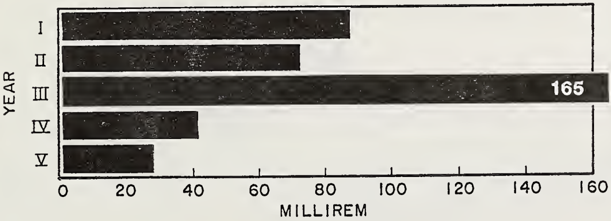


Figure 3: Mean Annual Radiation Dose for all Crew Leaders

Figure 4 shows mean annual radiation exposure for all panel operators. The dose level for all panel operators during Year I was 72 millirem which was about equal to the average exposure for all employees. Year II shows panel operators with the highest dose levels of the study. The mean radiation dose for this group was 330 millirem. One individual during Year II returned two monthly film badges which showed considerably higher doses (270 and 750 millirem) than the average for the group. To register these high doses the film badges may have been left directly on top of piping containing significant amounts of scale build-up. Without these high badge results the mean dose for Year II would have been about 85 millirem. Year III for panel operators showed a mean annual dose of 201 millirem. Monthly average dose levels during Year II consistently ranged between 10 and 20 millirem with one "outlier" of 40 millirem. Year IV showed significant reduction in dose levels for panel operators with a mean annual dose of 62 millirem. This trend continued through Year V with a further reduction in the mean annual dose down to 32 millirem.

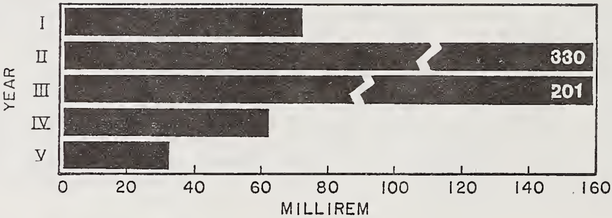


Figure 4: Mean Annual Radiation Dose for all Panel Operators

Figure 5 shows the data for tank farm operators with a fairly consistent rise in radiation doses from 47 millirem in Year I to 96 millirem in Year II and peaking in Year III with a mean annual dose of 158 millirem. As with other job classes (crew leaders and panel operators), there was a significant drop in radiation exposures following the clean-out of filtrate handling vessels. Annual mean radiation dose levels in Year IV and V for tank farm operators were 36 and 28 millirem respectively.

Figure 6 shows mean annual radiation dosages over the five year study for sulphuric acid operators. The data show a consistent rise in dose levels from Year I (49 millirem) to Year III with 103 millirem. Improvements to filtrate handling vessels brought dose levels down during Year IV to 44 millirem, and in Year V down to 12 millirem. This was to be expected as the sulphuric acid plant is separated from the phosphoric acid plant.

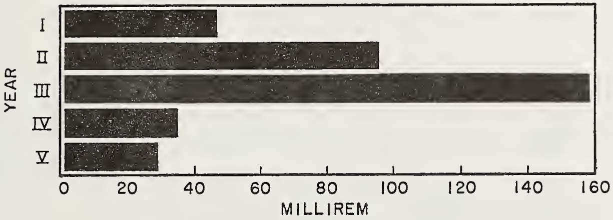


Figure 5: Mean Annual Radiation Dose for all Tank Farm Operators

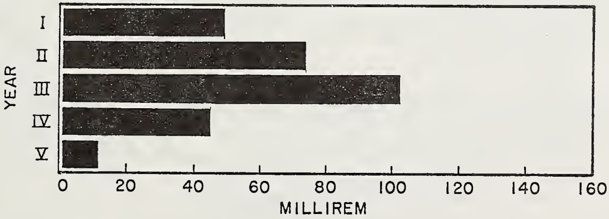


Figure 6: Mean Annual Radiation Dose for all Sulphuric Acid Operators

At the beginning of Year I an improved method of record keeping was instituted, tracking on a monthly basis the movement and replacement of people between crews at the phosphoric plant. This permitted a personal dose record to be kept for each employee who worked on the unit at any time during the year. The total annual dose for each employee during Years II and III are shown in the distribution histograms. During Year II film badges were worn on a monthly basis by 46 employees over periods ranging from one to eleven months. These results indicate that 95% of the doses received were 130 millirem or less, with 50% (23 of 46) registering no detectable dose. All of the yearly accumulated doses were well below the exposure criterion of 500 millirem per year with one exception at 1020 millirem. This high dose was primarily due to the two high film badge results mentioned previously.

During Year III film badges were worn by a total of 46 employees over periods ranging from one to twelve months. These results indicate that 98% of the doses received were less than 160 millirem (1/3 the 500 millirem exposure criterion). There was however a general rise in the dose received by all employees over that received during Year II. (Figure 7).

During Year IV film badges were worn by a total of 52 employees for periods ranging from 1 to 11 months. The results indicate that 98% of the doses received were less than 70 millirem. The distribution of doses for Year V shows slightly more exposures at less than 30 millirem compared with Year IV.

During the third quarter of Year II an additional monitoring technique was introduced whereby three extra film badges were mounted at various stations in the phosphoric acid plant. These badges were to act as fixed location dosimeters and were exposed continuously over the month integrating radiation exposures at these locations. The three work locations included the control panel, an area above the control room desk and on the control room blackboard. Monthly spot checks of radiation dose rates were also made at each location with a radiation survey meter. Agreement between the integrated dose measurement made by the film badges and the spot measurements was good.

Radiation dose rates, as monitored with the film badge and survey meter, at the control panel showed a stable dose rate between 0.05 and 0.10 millirem per hour during the study period (three and a quarter years).

Radiation dose rates above the control room desk monitored by the two methods showed a gradual decline over the monitoring period. During the last quarter of Year II and throughout Year III, radiation dose rates ranged between 0.3 and 0.4 millirem per hour. In Year IV and Year V they dropped to and remained below 0.2 millirem per hour.

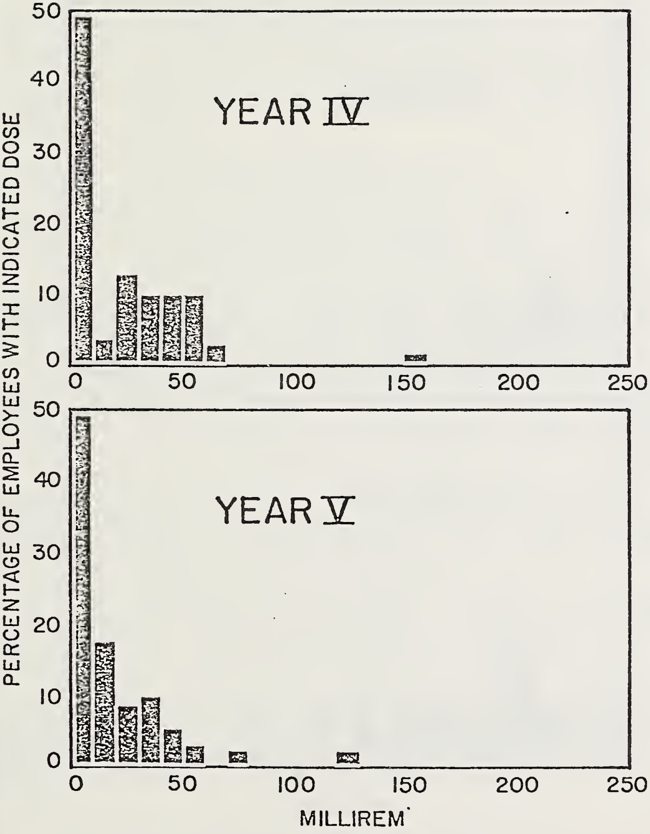


Figure 7: Distribution Histograms of Annual Radiation Dose of Each Employee

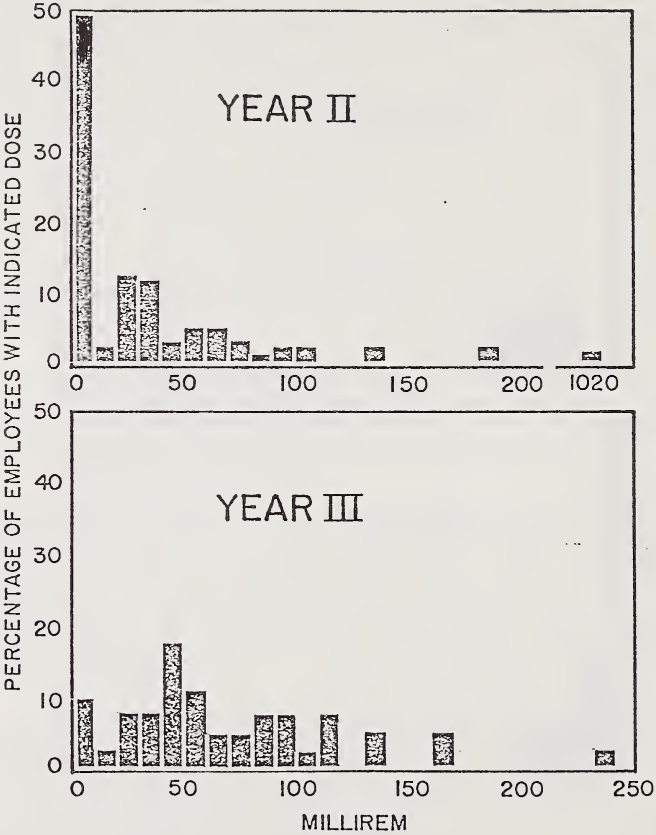


Figure 8: Distribution Histograms of Annual Radiation Dose of Each Employee

Radiation dose rates at the control room blackboard using these monitoring methods climbed from about 0.3 millirem to about 0.8 millirem during the last quarter of Year II. During Year III they remained around 1.0 millirem until the end of the first quarter in Year IV. During the second quarter of Year IV, following the clean-up of accumulated scale on filtrate pipes, radiation dose rates fell to between 0.1 and 0.2 millirem per hour and remained at these levels to the conclusion of the study. (Figure 8).

Assessment of radon and radon daughter levels

Monitoring of radon and radon daughter levels was conducted once during late spring and again in winter to determine potential employee exposures and to assess whether there was any build-up of these materials in the Phosphoric Acid Plant.

The Atomic Energy Control Act specifies the maximum permissible exposure to radon daughters for workers other than atomic radiation workers. This level is 0.4 Working Level Months (WLM) per year.

Measurements were made using a commercially available radon and radon daughter detector. Air samples were collected using a pump operating at a nominal flow rate of 5 litres per minute. Particulates were collected on 25 mm Type AA gridded membrane filters.

Calculations to arrive at working level were based on the modified Kusnetz Method. To obtain Working Level Months the average level was multiplied by an estimated exposure time (a person working five, twelve hour shifts per week per year) divided by 173 hours per month (52 weeks at 40 hours per week = 2080 hours per year = 173 hours per month).

Estimated exposures for various locations within the Phosphoric Acid Plant under both summer and winter conditions: all Working Level Month estimated exposures were much less than the 0.40 criteria adopted under the Atomic Energy Control Act.

The levels of radon 222 are not in themselves important as it is the radon daughters that are of significance to health. However, radon levels were measured in certain areas to provide information on the maximum levels of daughters which might be present and also to provide information on the ventilation in a given area. (Table I).

Conclusion

This paper presents the results of a five year monitoring study which showed gamma radiation exposure levels for operators working in the Phosphoric Acid Plant. Airborne radon and radon daughter concentrations are also given.

TABLE I: Estimated Exposures for Various Locations

Location	May	January	Radon pCi/L	Radon Daughters Working level months
Control room				
- sulphuric acid	✓		<1.1	<0.05
		✓	–	0.05
- phosphoric acid	✓		<0.8	<0.02
Filter wash area	✓		<1.3	<0.04
- phosphoric acid		✓	1.5	0.07

Radiation doses, recorded over a five year period, were well below the recommended exposure guideline of 500 millirem per annum for non-radiation workers. Radon daughter levels were well below the 0.4 Working Level Month guideline recommended by the Atomic Energy Control Board for non-atomic radiation workers.

MUTAGENICITY OF SOME ANILINE DERIVATIVES

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Abstract

Some aniline derivatives are widely used in chemical industries as the intermediate of dyestuffs or food additives. It is known that aniline has no mutagenic activity in the Ames test but it reveals mutagenicity in the presence of norharman which has no mutagenic activity itself. In our laboratory, mutagenicity of 9 aniline derivatives have been tested by using Salmonella typhimurium TA98, TA100, TA1538 and E. Coli WP2uvrA, WP2uvrA/pKM. Mutagenicity of 7 compounds (2,4-dinitroaniline, o-nitroaniline, 2-chloro-4-nitro-aniline , 2,4,6-trichloro-aniline, 2,4,6-trimethylaniline, p-methoxyaniline and m-phenylenediamine) was positive in Salmonella or E. Coli by the preincubation method but negative in 2 compounds (2-methoxy-5-methylaniline and o-ethylaniline). On the other hand, o-ethylaniline and 2-methoxy-5-methylaniline showed positive results in TA98 in the presence of norharman. The fluctuation test has been performed at the same time to examine mutagenicity of the same compounds using Salmonella typhimurium TA98. The results were same as those in the preincubation method except in the case of o-nitroaniline and p-methoxyaniline.

Résumé

Certains dérivés d'aniline sont grandement utilisés dans l'industrie chimique comme intermédiaires des teintures ou des additifs alimentaires. Il est reconnu que l'aniline ne produit pas d'activité mutagène avec l'épreuve de Ames mais qu'elle présente une mutagénicité en présence de norharman qui ne possède pas d'activité mutagène en soi. Dans notre laboratoire, la mutagénicité de 9 dérivés de l'aniline a été étudiée en utilisant Salmonella typhimurium TA98, TA100, TA1538 et E. Coli WP2uvrA, WP2uvrA/pKM. La mutagénicité de 7 composés (2,4-dinitroaniline, o-nitroaniline, 2-chloro-4-nitroaniline, 2,4,6-trichloroaniline, 2,4,6-triméthyl- aniline, p-méthoxyaniline and m-phénylénédiamine) était positive chez Salmonella ou E. Coli par le méthode de préincubation mais négative pour 2 composés (2-méthoxy-5-méthylaniline and o-éthylaniline).

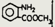
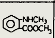
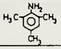
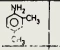
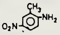
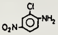
D'autre part, o-éthylaniline et 2-méthoxy-5-méthylaniline ont donné des résultats positifs pour TA98 en présence de norharman. Les épreuves de fluctuation ont été effectuées en même temps pour étudier la mutagénicité des mêmes composés en utilisant Salmonella typhimurium TA98. Les résultats étaient les mêmes que ceux obtenus avec la méthode de préincubation sauf dans le cas de o-nitroaniline and p-méthoxyaniline.

Aniline and its derivatives are widely used as the intermediates of dyestuffs. It has been believed that pure aniline is not carcinogenic to human subjects. Recently it has been reported by the National Cancer Institute of the U.S. that Fisher 344 rats given a diet containing aniline hydrochloride produced hemangiosarcomas or fibrosarcomas of the spleen (1). Aniline does not show any mutagenicity in the Ames test, but the mutagenicity of aniline was demonstrated by Nageo et al. (2) in the presence of norharman and S9 mix using Salmonella typhimurium TA98, although norharman itself was found to be nonmutagenic.

We tested the mutagenicity of nineteen aniline derivatives shown in Table 1 by the assay and also examined the comutagenic effect of norharman. The mutation test was performed by the modified preincubation method (3) of the Ames assay (4) using the test strains of Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538, TA97, TA2637, E. Coli WP2uvrA and E. Coli WP2uvrA/pKM.

According to the results of mutagenic and commutagenic activities, these aniline derivatives were divided into seven groups. As shown in Table 1, the derivatives in the first group, compounds No. 1, No. 2 and No. 3, did not show mutagenicity, and also the comutagenic action of norharman was not seen in these derivatives. The derivatives in the second group, compounds No. 4 and No. 5, did not show mutagenicity but the comutagenic action of norharman was observed. The derivatives in the third group, compounds No. 6 and No. 10, did not show mutagenicity but the comutagenic action of norharman was remarkable. The derivatives in the fourth group, compounds No. 11 and No. 12, showed mutagenicity but the comutagenic action of norharman was not observed. The derivatives in the fifth group, compounds No. 13 and No. 14, showed mutagenicity and also the comutagenic action of norharman was observed. The derivatives in the sixth group, compounds No. 15, No. 16, No. 17, showed mutagenicity and remarkable comutagenic action of norharman was seen. The derivatives in the seventh group, compounds No. 18 and No. 19, showed strong mutagenicity and also remarkable comutagenic activities in the presence of norharman. The carcinogenicity of most these aniline derivatives are unknown. It has been reported that compounds No. 7, No. 10 and No. 19 are noncarcinogenic (5,6,7,8) and compounds No. 11, No. 12, No. 13, and No. 17 are carcinogenic (8,9) to experimental animals.

TABLE 1: Mutagenicity of Aniline Derivatives

No.	COMPOUND	CHEMICAL STRUCTURE	Carcinogenicity	Mutagenicity	Mutagenic activity (His$^+$/mg)			
					TA100	TA98	others	TA98 norharman
1	metanilic acid		?	-	0	0	0	0
2	p-toluidine-m-sulfonic acid		?	-	0	0	0	0
3	4-methyl-2-nitroaniline		?	-	0	0	0	0
4	anthranilic acid methylester		?	-	0	0	0	4.0×10^2
5	2-methoxy-5-methylaniline(p-cresidine)		?	-	0	0	0	4.3×10^2
6	N-methylanthranilic acid methylester		?	-	0	0	0	1.1×10^3
7	N,N-dimethylaniline		-	-	0	0	0	6.3×10^3
8	N,N-diethylaniline		?	-	0	0	0	3.5×10^4
9	o-ethylaniline		?	-	0	0	0	3.8×10^5
10	N-methylaniline		-	-	0	0	0	7.4×10^5
11	2,4,6-trichloroaniline		+	+	0	0	2.7×10^1	0
12	2,4,6-trimethylaniline(mesidine)		+	+	1.6×10^3	1.2×10^1	4.4×10^2	0
13	2,4-xylidine		+	+	6.2×10^2	1.4×10^1	3.4×10^2	7.7×10^1
14	o-nitroaniline		?	+	1.8×10^1	4.8×10^1	4.2×10^1	1.8×10^2
15	2-methyl-4-nitroaniline		?	+	0	0	7.6×10^1	1.6×10^3
16	2-chloro-4-nitroaniline		?	+	0	9.9×10^1	5.3×10^2	2.0×10^3
17	o-methoxyaniline(o-anisidine)		+	+	0	7.9×10^1	9.3×10^1	2.0×10^4
18	2,4-dinitroaniline		?	+	7.4×10^2	1.8×10^3	5.0×10^1	1.1×10^4
19	m-phenylenediamine		-	+	3.7×10^2	9.4×10^3	5.2×10^1	4.0×10^4

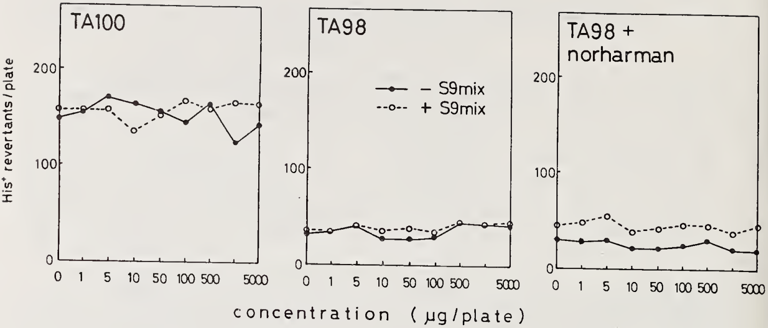


Figure 1: The Dose-Response Curves of Mutation of Metanilic Acid

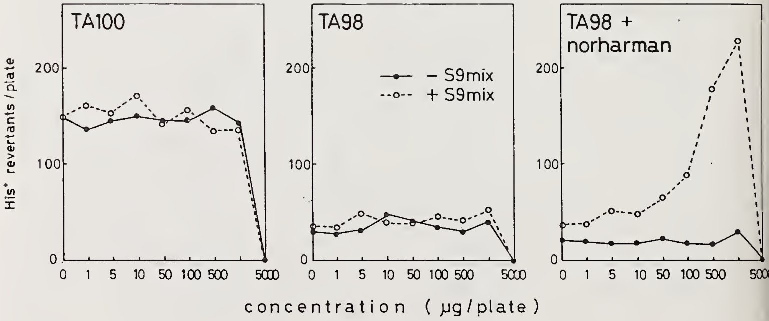


Figure 2: The Dose-Response Curves of Mutation of Anthranilic Acid Methylester

The dose-response curves of mutation of metanilic acid in the first group are shown in Figure 1. The number of His+ revertants per plate with S9 mix (the dotted line) or without S9 mix (the solid line) are ploted against the dose of the chemical. Metanilic acid was not mutagenic on TA100 and TA98. It was not mutagenic on TA98 even in the presence of norharman. Similar results were seen in p-toluidine-m-sulfonic acid and 4-methyl-2-nitroaniline.

The dose-response curves of mutation of anthranilic acid methylester in the second group are shown in Figure 2. Anthranilic acid ester was not mutagenic on TA100 and on TA98 but mutagenic on TA98 in the presence of norharman and S9 mix. Similar results were observed in 2-methoxy-5-methylaniline.

Figure 3 shows the results of o-ethylaniline in the third group. o-ethylaniline was not mutagenic on TA100 and on TA98 but it showed very strong mutagenic activity on TA98 in the presence of norharman, as seen by the number of revertant colonies per plate. Similar results were obtained in N-methylanthranilic acid methyl-ester, N,N-dimethylaniline, N,N-diethlaniline and N-methylaniline.

The results of 2,4,6-trimethylaniline in the fourth group are shown in Figure 4. 2,4,6-Trimethylaniline was mutagenic on TA100, E. Coli WP2uvrA and WP2uvrA/pKM but it did not show mutagenic activity on TA98 with or without norharman. Similarly, 2,4,6-trichloroaniline was mutagenic on TA1538 but not mutagenic on TA98 with and without norharman.

The results of 2,4-xylidine in the fifth group are shown in Figure 5. 2,4-xylidine showed weak mutagenicity on TA100 but did not on TA98. However it showed mutagenic activity on TA98 in the presence of norharman. Similar results were seen in o-nitroaniline.

The results of o-methoxyaniline in the sixth group are shown in Figure 6. o-methoxyaniline was mutagenic on TA100. In the presence of norharman it was mutagenic on TA98. Similar results were seen in 2-chloro-4-nitroaniline. 2-Methyl-4-nitroaniline was also mutagenic on TA1535, and in the presence of norharman it was mutagenic on TA98.

Figure 7 shows the results of m-phenylenediamine in the seventh group. m-Phenylenediamine showed mutagenic activity on TA100 and very strong mutagenicity on TA98 with and without norharman. Similar results were observed in 2,4-dinitroaniline.

The details of the results of our experiments are shown in Table 1. All the mutagenic compounds required activation by S9 mix. Mutagenicity of compounds No. 11 to No. 19 was significant. Especially 2,4-dinitroaniline and m-phenylenediamine showed strong mutagenic activities. Mutagenicity of compounds No. 6 to No. 10 was negative, but in the presence of norharman mutagenicity was highly significant.

Aniline or o-toluidine is nonmutagenic, but by the comutagenic action of norharman these compounds reveal strong mutagenicity, although norharman itself in nonmutagenic. Such mutagens activated by norharman required metabolic activation by S9 mix. Figure 8 shows the chemical structure of norharman. Norharman was found in the tryptophan pyrolysate, and in our environment a small amount of norharman was detected in the charred material on the surface of broiled fish or meat and in tobacco tar and wine (10). In our experiments, aniline derivatives such as compounds No. 6 to No. 10, which are nonmutagenic, revealed strong mutagenicity by the comutagenic action of norharman. It is arguable whether the comutagenic action of norharman observed in vitro also arises in vivo.

In 1895, Rehn found the first occupational bladder cancer in workers exposed to aniline in the dyestuff factories. He thought that this occupational bladder cancer was caused by aniline. Recently it has been reported that aniline hydrochloride is carcinogenic to Fisher 344 rats, but today it is believed that pure aniline is not carcinogenic to human subjects. As mentioned above, some aniline derivatives are mutagenic in the microbial mutation test, but it is questionable whether aniline derivatives are carcinogenic to human subjects.

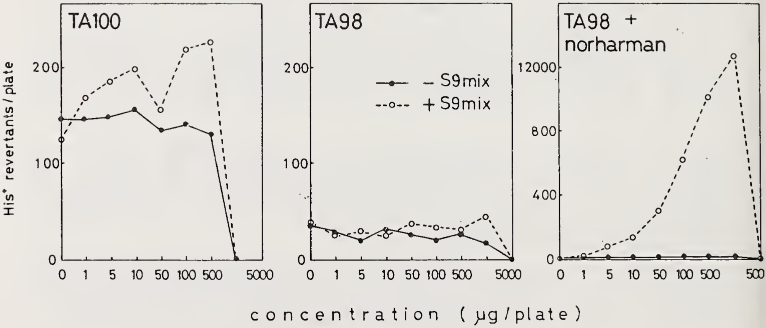


Figure 3: The Dose-Response Curves of Mutation of o-Ethylaniline

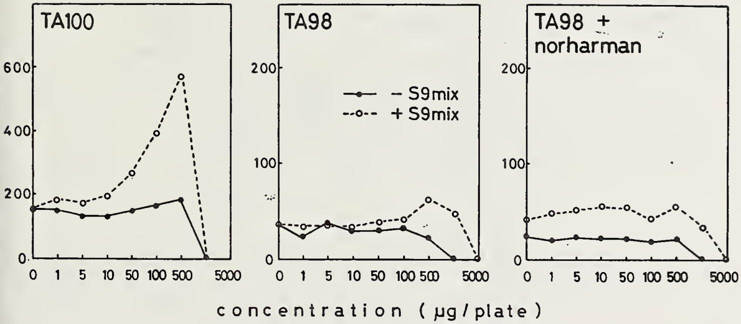


Figure 4: The Dose-Response Curves of Mutation of 2,4,6,-Trimethylaniline

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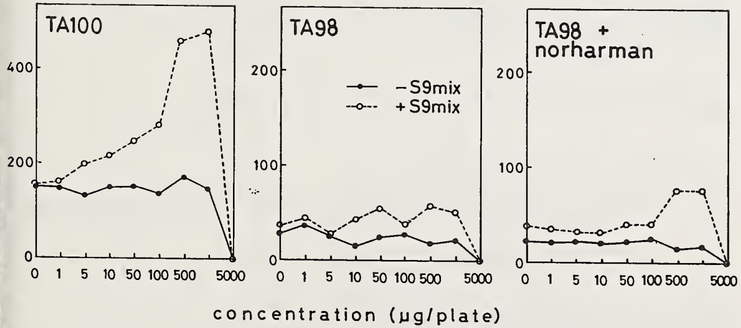

Figure 5: The Dose-Response Curves of Mutation of 2,4-Xylidine

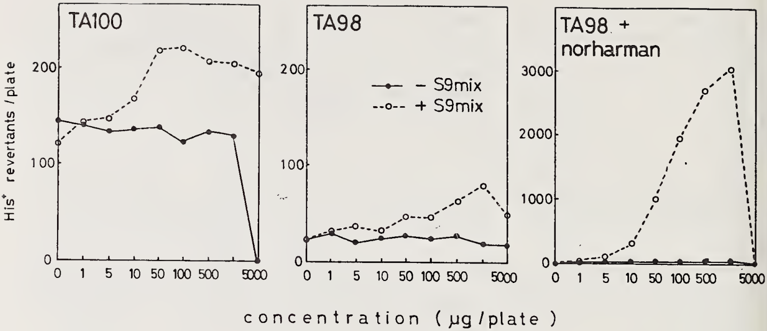

Figure 6: The Dose-Response Curves of Mutation of o-Methoxyaniline

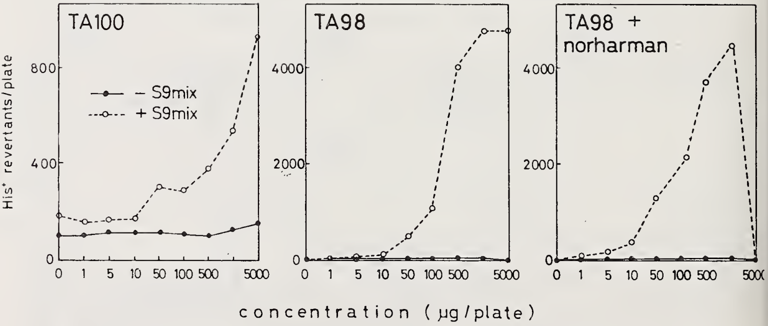

Figure 7: The Dose-Response Curves of Mutation of m-Phenylenediamine

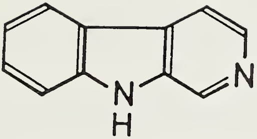

Figure 8: The Chemical Structure of Norharman

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CLOSING ADDRESS

CLOSING ADDRESS

A. M. Thiess
MEDICHEM Chairman

Ladies and Gentlemen,

After a three day conference, it is now time to close our gathering here in Calgary.

The goal of MEDICHEM's XIth International Congress has been the bringing on of an exchange of views of the topics:

1. OCCUPATIONAL HEALTH AND TOXICOLOGICAL PROBLEMS IN THE PETROLEUM, GAS AND PETROCHEMICAL INDUSTRIES;

2. EMERGENCIES IN THE CHEMICAL INDUSTRY: ASSESSMENT AND INTERVENTION;

3. APPLICATIONS OF COMPUTER TECHNOLOGY IN OCCUPATIONAL HEALTH; and

4. CURRENT OCCUPATIONAL HEALTH PROBLEMS IN THE CHEMICAL INDUSTRY.

The total programme drew 162 registered and 40 accompanying persons from 20 countries, and listed over 40 papers. We had fruitful discussions and interesting questions following the excellent presentations. Owing to a perfectly working organization, it has been a pleasure to attend this conference, and the proceedings will document this.

May I take this opportunity to express my deep appreciation on behalf of all of you, to those colleagues who prepared a paper and also to those who with their critical comments successfully contributed to the topics. Many thanks also to the session leaders, the interpreters, the technical personnel, and all the others who were busy behind the curtain, and last but not least to all of you who have attended this conference.

Gratefully, we all congratulate Dr. Orford and Dr. Cowell for the excellent organization. Both of you have done a very good job. When going home, we will be satisfied with this MEDICHEM conference, and that is the highest praise you can get. Thanks also for the pleasant social programme. Calgary has met all our expectations in every respect.

We know that you, Dr. Orford and Dr. Cowell, have spent so much of your spare time in order to work for this conference.

So the Board of MEDICHEM is glad to present you this small gif which should always remind you of this successful congress. Th bouquets of flowers are for your spouses, with many thanks.

As our Secretary, Dr. D.F. Rijkels, decided to resig irrevocably, I would like to thank him also for his work Together with his secretariat, he has helped MEDICHEM t continue its endeavours to be the link in the big MEDICHE family. Please accept this present which Brigitta brought ove from Sweden in remembrance of your commitment to MEDICHEM.

As you all know, the XIIth MEDICHEM Congress will be hel in Dublin, Ireland, on September 11 and 12, 1984, within th framework of the XXIst Permanent Commission Congress o Occupational Health being held from September 9-14, 1983. hall for 250 persons will be provided for MEDICHEM, and MEDICHE will publish separate proceedings. Our contact person will b Dr. Dan Murphy from the Department of Labour in Dublin.

The Board's decision is that only the following two topic should be discussed and presented during the sessions in orde to increase the scientific value of MEDICHEM:

1. Mixed Exposure and Multiple Factor Interaction in th Chemical Industry and,

2. Assessment of Reproductive Hazards in the Workplace.

The topic "Current Occupational Health Problems" will als be added for this Congress.

All the abstracts should be submitted by the end of Januar 1984. They all will be reviewed by a commission of experts MEDICHEM would highly appreciate your attendance with presentation.

For 1985, the Board has followed the invitation from Dr Estrela to hold the MEDICHEM conference from September 9-12 i Salvador and Camacari, Bahia. This decision has been made fo two reasons. Firstly, it is in the spirit of MEDICHEM t explore other continents, and this will be the first time th Congress is to be held in South America. Secondly, there ar about 30 chemical firms located in Salvador and Camacari. Th topics will be decided during the Dublin Conference.

In 1986, also in September, the XIVth MEDICHEM Congres will be held in Ludwigshafen, where the founding of MEDICHE took place in 1972, and where MEDICHEM's cradle is. The reaso is that it will be the present Chairman's time to announce hi retirement.

More details will be mailed through our MEDICHE Newsletter. At the end of a time so successfully spent amon friends here in Calgary, let me say once again, many thanks to all our hosts and I wish you all a warm good-bye, and happy landings.

- So Long
- Au Revoir
- Arrivederci
- Hasta Luego
- Tot Ziens
- Adjö, so Länge
- Farvel
- Sayonara, and
- Auf Wiedersehen

in good health in Dublin in 1984.

The XIth MEDICHEM Congress is closed.

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